IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of David T. Scadden et al. Serial No.: 08/447,314 Filed: 22 May 1995 For: PROTEIN TYROSINE KINASES	Group Art Unit: 1812 Examiner: S. Teng CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on Nov. 6, 1997 Joyce Cohen Joyce Cohen

DECLARATION PURSUANT TO 37 CFR §1.131

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

The undersigned, do hereby declare and say as follows:

1. We are joint inventors of the subject matter of the above-identified patent application. All work described in this declaration was performed by us or on our behalf in the United States of America.

2. We have read and understood the Office Action dated August 6, 1996, rejecting claims under 35 U.S.C. 103 over Johnson et. al. in this application. The Johnson et. al. article is believed to have a publication date in June 1993.

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11. CHO clones expressing a fusion protein corresponding to the HPTK6-IgG fusion construct were selected, individual clones were isolated and then checked for production of the fusion protein. See Exhibit G.

12. Each of the dates deleted from Exhibits A-G is prior to June, 1993.

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25. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements where made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE

DAVID T. SCADDEN

10/30/97

DATE

KEVIN P. BAKER

DATE

WILL F. BARON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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DATE	KEVIN P. BAKER
10/29/97 DATE	Will F. Baron WILL F. BARON

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11/4/97
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DAVID T. SCADDEN

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KEVIN P. BAKER

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WILL F. BARON

Hybritech Incorporated v. Monoclonal Antibodies, Inc.

U.S. Court of Appeals Federal Circuit
231 USPQ 81

Decided September 19, 1986
No. 86-531

Headnotes

PATENTS

1. Patentability/Validity -- Date of invention -- Conception (§ 115.0403)

Federal district court's finding that evidence was lacking as to when, before May 1980, claimed invention of using monoclonal antibodies in "sandwich" assays was conceived by patent holder, is clearly erroneous, in view of evidence demonstrating patent holder's earlier efforts in developing claimed invention by using prior art technology to produce necessary monoclonal antibodies in diagnostic sandwich assay kits, in view of evidence demonstrating that exploiting monoclonal antibodies for use in sandwich assays was one of patent holder's major objectives, and in view of laboratory notebooks and research program that fully corroborate testimonial evidence of conception, since such evidence clearly supports holding that patent holder conceived claimed invention before patent challenger and that patent challenger's work is not prior art.

2. Patentability/Validity -- Anticipation -- Identity of elements (§ 115.0704)

Prior art work that involved "sandwich" assay to extent that antigen was sandwiched between two monoclonal antibodies, but that did not involve detecting presence of or quantitating antigen,

did not anticipate claimed invention, since it did not meet its every element.

3. Patentability/Validity -- Obviousness -- Relevant prior art -- Particular inventions (§ 115.0903.03)

Articles which "predicted" widespread use of monoclonal antibodies but which are dated well after patented monoclonal assay's date of conception and within one year of its filing date, are not prior art, nor should earlier articles which discussed production of monoclonal antibodies, although clearly prior art, have been relied upon to establish obviousness of trying monoclonal antibodies of particular affinity in "sandwich" immunoassay that detects presence of or quantitates antigen, since such articles do not suggest how that end may be accomplished, and since "obvious to try" is improper consideration in adjudicating obviousness issue.

4. Patentability/Validity -- Obviousness -- Commercial success (§ 115.0908)

Trial court's finding that "sudden availability" of monoclonals was reason for commercial success of patented diagnostic kits is clearly erroneous, in view of evidence demonstrating that at least three years passed between time monoclonal antibodies were available in adequate supply and time patent holder began selling its kits.

5. Patentability/Validity -- Specification -- Claim adequacy (§ 115.1109)

Federal district court erred in holding that claims for monoclonal assay are indefinite because antibody affinity cannot be estimated with any consistency, since calculating affinity was known in art at time of filing, and since such claims reasonably apprise those skilled in art and are as precise as subject matter permits, even though calculations are not precise or "standard."

Particular patents -- Assays

4,376,110, David and Green, Immunometric Assays Using Monoclonal Antibodies, holding of invalidity reversed.

Case History and Disposition:

Appeal from District Court for the Northern District of California, Conti, J.; 227 USPQ 215 .

Action by Hybritech Incorporated, against Monoclonal Antibodies, Inc., for patent infringement. From judgment for defendant, plaintiff appeals. Reversed and remanded.

Attorneys:

Douglas E. Olson, and Lyon & Lyon, both of Los Angeles, Calif. (James W. Geriak and Bradford J. Duft, both of Los Angeles, Calif., on the brief) for appellant.

David J. Brezner, and Flehr, Hohback, Test, Albritton & Herbert, both of San Francisco, Calif. (Barry E. Britschneider and Herbert I. Cantor, both of Washington, D.C., of counsel) for appellee.

Judge:

Before Rich, Davis, and Smith, Circuit Judges.

Opinion Text

Opinion By:

Rich, Circuit Judge.

This appeal is from the August 28, 1985, decision of the United States District Court for the Northern District of California, 623 F.Supp. 1344, 227 USPQ 215 , in favor of defendant Monoclonal Antibodies, Inc. (Monoclonal) holding that all 29 claims of plaintiff's patent No. 4,376,110 entitled "Immunometric Assays Using Monoclonal Antibodies" ('110 patent), issued to Dr. Gary S. David and Howard E. Greene and assigned to Hybritech Incorporated (Hybritech), are invalid as anticipated under 35 USC 102(g), for obvious

ness under §103, and under §112 first and second paragraphs. We reverse and remand.

Background

Vetebrates defend themselves against invasion by microorganisms by producing antibodies, proteins which can complex with the invading microorganisms and target them for destruction or removal. In fact, any foreign molecule of sufficient size can act as a stimulus for antibody production. Such foreign molecules, or antigens, bear particular sites or epitopes that represent antibody recognition sites. B cell lymphocytes, the cells that actually produce antibodies, recognize and respond to an epitope on an antigen by reproducing or cloning themselves and then

producing antibodies specific to that epitope. Even if the antigen is highly purified, the lymphocytes will produce antibodies specific to different epitopes on the antigen and so produce antibodies with different specificities. Furthermore, because the body is exposed to many different antigens, the blood of a vertebrate will contain antibodies to many different antigenic substances.

Scientists and clinicians have long employed the ability of antibodies to recognize and complex with antigens as a tool to identify or label particular cells or molecules and to separate them from a mixture. Their source of antibodies has been primarily the serum separated from the blood of a vertebrate immunized or exposed to the antigen. Serum, however, contains a mixture of antibodies directed to numerous antigens and to any number of epitopes on a particular antigen. Because such a mixture of antibodies arises from many different clones of lymphocytes, it is called "polyclonal."

Recent technological advances have made it possible to isolate and cultivate a single clone of lymphocytes to obtain a virtually unlimited supply of antibodies specific to one particular epitope. These antibodies, known as "monoclonal antibodies" because they arise from a single clone of lymphocytes, are produced by a relatively new technology known as the hybridoma. Hybridomas are produced by fusing a particular cancer cell, the myeloma cell, with spleen cells from a mouse that has been injected or immunized with the antigen. These fusions are isolated by transferring them to a growth fluid that kills off the unfused cancer cells, the unfused spleen cells dying off by themselves. The fused hybrid spleen and myeloma cells, called hybridomas, produce antibodies to the antigen initially injected into the mouse. The growth fluid containing the hybridomas is then diluted and put into individual test tubes or wells so that there is only one hybridoma per tube or well. Each hybridoma then reproduces itself and these identical hybridomas each produce identical monoclonal antibodies having the same affinity and specificity. In this way, a virtually unlimited supply of identical antibodies is created, directed to only one epitope on an antigen rather than, as with polyclonal antibodies, to many different epitopes on many different antigens.

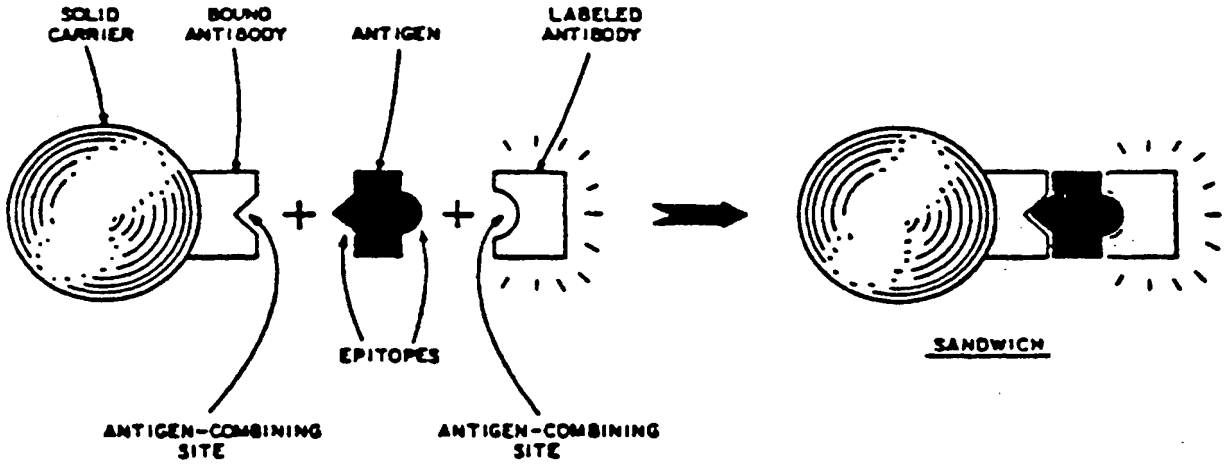
In addition to the specificity of antibodies to particular epitopes discussed above, antibodies also have a characteristic "sensitivity," the ability to detect and react to antigens. Sensitivity is expressed in terms of "affinity:" the greater an antibody's ability to bind with a particular antigen, the greater the antibody's affinity. The strength of that antibody-antigen bond is in part dependent upon the antibody's "affinity constant," expressed in liters per mole, for the antigen.

Immunoassays, the subject matter of the '110 patent are diagnostic methods for determining the presence or amount of antigen in body fluids such as blood or urine by employing the ability of an antibody to recognize and bind to an antigen. Generally, the extent to which the antibody binds to the antigen to be quantitated is an indication of the amount of antigen present in the fluid. Labelling the antibody or, in some cases, the antigen, with either a radioactive substance, I^{125}, or an enzyme makes possible the detection of the antibody-antigen complex. In an extreme case, where the fluid sample contains a very low level of the antigen, binding might not occur unless the antibodies selected or "screened" for the procedure are highly sensitive.

In the case of a "competitive" immunoassay, a labelled antigen reagent is bound to a limited and known quantity of antibody reagent. After that reaction reaches equilibrium, the antigen to be detected is added to the mixture and competes with the labelled antigen for the limited number of antibody binding sites. The amount of labelled antigen reagent displaced, if any, in this second reaction indicates the quantity of the antigen to be detected present in the fluid sample. All of the antigen attached to the antibody will be labelled antigen if there is no antigen in the test fluid sample. The advantage of this method is that only a small amount of antibody is needed, its drawback, generally, that the system must reach equilibrium, and thus produces results slowly.

In the case of a "sandwich" assay, otherwise known as an immunometric assay, the latter being a term coined by Dr. Lawton Miles in 1971, a quantity of unlabelled antibody reagent is bound to a solid support surface such as the inside wall of a test tube containing a complex of the fluid sample containing the

antigen to be detected and a labelled *antibody* reagent. The result is an insoluble three part complex referred to as a sandwich having antibody bread and antigen filling. This figure is illustrative of the sandwich concept:



The advantage of the sandwich assay is that it is fast and simple, its drawback that enormous quantities of antibodies are needed.

Hybritech

Hybritech, started in 1978 and joined thereafter by coinventors Green and Dr. David, has, since 1979, been in the business of developing diagnostic kits employing monoclonal antibodies that detect numerous antigens and thus a broad range of conditions such as pregnancy, cancer, growth hormone deficiency, or hepatitis. Examples of antigens include influenza viruses, immunoglobulin E (IgE) which indicates allergic reaction, human chorionic gonadotropin (HCG)

which indicates pregnancy, and prostatic acid phosphatase (PAP) which indicates prostate cancer, to name a few. Dr. Adams, a business-experienced scientist, joined the company in May 1980 as head of research and development. The '110 patent, application for which was filed August 4, 1980, issued March 8, 1983, with claims defining a variety of sandwich assays using monoclonal antibodies. Claim 19, apparently the broadest of the twenty-nine in the patent, is directed generally to a sandwich assay and reads (emphasis ours):

> 19. In *an immunometric assay* to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, *the improvement comprising* employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10^{8} liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.

Claim 1, directed particularly to a reverse sandwich assay, explained infra, reads:

> 1. A process for the determination of the presence of [sic, or] concentration of an antigenic substance in a fluid comprising the steps:
>
> (a) contacting a sample of the fluid with a measured amount of a soluble first monoclonal antibody to the antigenic substance in order to form a soluble complex of the antibody and antigenic substance present in said sample, said first monoclonal antibody being labelled;
>
> (b) contacting the soluble complex with a second monoclonal antibody to the antigenic substance, said second monoclonal antibody being bound to a solid carrier, said solid carrier being insoluble in said fluid, in order to form an insoluble complex of said first monoclonal antibody, said antigenic substance and said second monoclonal antibody bound to said solid carrier;
>
> (c) separating said solid carrier from the fluid sample and unreacted labelled antibody;
>
> (d) measuring either the amount of labelled antibody; associated with the solid carrier or the amount of unreacted labelled antibody; and
>
> (e) relating the amount of labelled antibody measured with the amount of labelled antibody measured for a control sample prepared in accordance with steps (a)-(d), said control sample being known to be free of said anti-genic substance, to determine the presence of antigenic substance in said fluid sample, or relating the amount of labelled antibody measured with the amount of labelled antibody measured for samples containing known amounts of antigenic substance prepared in accordance with steps (a)-(d) to determine the concentration of antigenic

substance in said fluid sample, the first and second monoclonal antibodies having an affinity for the antigenic substance of at least about 10 ^{8}liters/mole.

The District Court Decision

Hybritech sued Monoclonal March 2, 1984, for damages and an injunction alleging that the manufacture and sale of Monoclonal's diagnostic kits infringed the '110 patent. Trial without a jury began on August 5, 1985, and concluded August 23, 1985, thirty witnesses having been heard and over 2,000 pages of transcript generated. The district court produced the reported opinion, findings, and con

clusions, which use nearly verbatim Monoclonal's *pre-trial* brief and *pre-trial proposed* findings of fact and conclusions of law, in three days, in support of the judgment now on appeal.

The district court held that the claimed subject matter of the '110 patent was neither conceived nor actually reduced to practice before May 1980, and was anticipated under §102(g) by the actual reduction to practice of the invention by Drs. Uotila and Ruoslahti at the La Jolla Cancer Research Foundation (LJCRF) as early as November of 1979 and by the actual reduction to practice of the invention by Drs. Oi and Herzenberg (Oi/Herzenberg work) at the Stanford University Laboratory as early as July 1978, later published in December of 1979.

The district court also held the claims of the '110 patent invalid for obviousness from the Oi/Herzenberg work in view of (1) a February 1979 article by M. E. Frankel and W. Gerhard (Frankel article) which discloses high-affinity monoclonal antibodies, and apparently in view of numerous other references including (2) the work of Nobel Prize winners G. Kohler and C. Milstein disclosing a Nobel Prize-worthy method for producing monoclonal antibodies in vitro (outside the body) published in an August 7, 1975, article; (3) U.S. Patent No. 4,244,940 issued to Jeong et al. disclosing a simultaneous polyclonal assay (Jeong), U.S. Patent No. 4,098,876 to Piasio et al. disclosing a reverse polyclonal sandwich assay (Piasio), U.S. Patent No. 4,016,143 to Schurrs et al. disclosing a forward polyclonal sandwich assay (Schurrs); (4) a July 1979 publication by A. C. Cuello et al. disclosing the use of monoclonal antibodies in competitive assays; and (5) eight articles dated between January 1979 and March 6, 1980, "predicting" that monoclonal antibodies would be used in future immunoassays. 1

The district court also invalidated the patent on various grounds based on 35 USC 112, first and second paragraphs, as hereinafter discussed.

A. The References

1. Kohler and Milstein's Nobel Prize-Winning Work: Producing Monoclonal Antibodies In Vitro For the First Time

In early immunoassay work, polyclonal antibodies produced in vivo (in the body) in mice

were used to bind with the antigen to be detected in the body fluid sample. Mice were immunized by injection with antigen so that the lymphocytes in their bodies produced antibodies that attacked the injected antigen. Those polyclonal antibodies were withdrawn from the animal's blood and used in immunoassays. The major problem was that when the mice's immune systems changed or the mice died, the antibodies changed or died too; supply was limited and uncertain.

As the examiner was aware, Kohler and Milstein developed a technique not only for producing antibodies in vitro, independent of a living body, thus eliminating dependence on a particular animal, but for in vitro production of monoclonal antibodies by hybridomas, discussed in the Background section, supra.

Given that sandwich assays require enormous amounts of antibodies, companies like appellant and appellee, which utilize monoclonal antibodies for sandwich assays, would not be in business were it not for the work of Kohler and Milstein.

2. *The Work of Drs. Ruoslahti, Uotila, and Engvall at the La Jolla Cancer Research Foundation (LJCRF) in 1979 and 1980*

Dr. Ruoslahti performed mostly competitive immunoassays using polyclonal antibodies to alphafetoprotein (AFP) antigens at the City of Hope since 1970. Dr. Uotila joined him in late 1978 to perform immunoassays using monoclonal antibodies to AFP. After producing monoclonal antibodies to AFP and performing competitive radio immunoassays (RIA -- a competitive assay that uses a radioactive label) with monoclonal antibodies at the City of Hope in mid-1979, Drs. Ruoslahti, Uotila and Engvall left LJCRF.

In the fall of 1979, September or October according to Dr. Uotila, discussion and work began on using monoclonal antibodies to AFP in a sandwich assay. Dr. Uotila, the principal researcher in this particular endeavor, generated six notebooks while at the City of Hope and LJCRF. The next-to-last page of notebook four contained a note to Dr. Uotila from Dr. Ruoslahti reading:

> Sometime you should enzyme label a good monoclonal antibody so that you can set up a sandwich assay. If you use two monoclonal antibodies, you may be able to do the assay with a single incubation, since the monoclonal antibodies are likely to be

> directed against different determinants and not compete with one another.

Although Dr. Uotila's notebook pages were, for the most part, unsigned, undated, and uncorroborated, Dr. Ruoslahti's testimony, placed the date of this note at about October 1979 by referring to the first pages of notebook five which were dated in early November 1979. Dr. Ruoslahti testified that one curve on one graph on page 43D of notebook five showed a successful simultaneous sandwich assay using monoclonal antibodies about November 5, 1979, although no data supporting that graph could be found elsewhere in the notebook. He further

testified that the affinity of the monoclonal antibodies used for that test was not calculated until 1980 but that the raw data necessary for that calculation was generated in 1979.

Dr. Uotila stated in her deposition (she did not testify at trial) that she started work on a sandwich assay using monoclonal antibodies between October 4 and the end of that month, 1979, and that she could not remember the procedure used nor was there enough information in her notebook, including page 43D, to refresh her memory. She did remember, although she continued work on this assay because the tests did not yield repeatedly good curves without which she would not publish her work, that the assay on page 43D was successful. Dr. Engvall testified about a discussion of Dr. Uotila's monoclonal antibody work with her while at the City of Hope and about first performing a sandwich assay after arriving at LJCRF in 1979.

3. *The Work of Drs. Oi and Herzenberg at the Stanford University Laboratory in 1978 Published in December 1979*

Drs. Oi and Herzenberg used monoclonal antibodies to "map" epitopes or determine the number and location of different antibody binding sites on a known quantity of IgE antigen by attaching to it an antibody bound to a carrier and exposing that antigen to other monoclonal antibodies. The antibodies either attached to epitopes on the antigen or were blocked from doing so by the other monoclonal antibodies, depending on the location and number of epitopes; if the epitopes on the antigen were too close together and the number of antibodies too great, few antibodies would bind to the antigen. Hybritech points out that both Dr. Herzenberg and Dr. Oi testified that *their work did not involve determining the presence or quantity of antigen,* that they had no idea what the affinities of the monoclonal antibodies used were, and that those values were never calculated.

One unsigned, unwitnessed page from three large laboratory notebooks, which Hybritech argues is insufficient because it does not identify the chemical reagents or protocol used, was relied on by Monoclonal to establish actual reduction to practice of the Oi/Herzenberg work in 1978 to establish a case of §102(g) prior invention by another. The district court agreed with Monoclonal that the Oi/Herzenberg work anticipated the claimed invention and, in addition, combined this work with the Frankel publication to hold that the claimed subject matter was obvious under §103.

4. *The Frankel Article: Monoclonal Antibodies Having Affinities of 10 ^{9}liters/mole*

Frankel describes an RIA (radioimmunoassay) method for the rapid determination of affinity constants for monoclonal antibodies produced from hybridomas. The article states that the assay used is applicable only to antibodies with binding constants of about 10 ^{10}liters/mole and discloses the binding constants for antibodies to several closely related strains of influenza virus.

The district court found that Frankel disclosed monoclonal antibodies having the affinity constants claimed in the '110 patent, 10 ^{8}to over 10 ^{9}liters/mole.

5. *The Cuello Article and the Jeong, Piasio, and Schurr Patents Considered by the Examiner*

Cuello, dated July 1979, states that it describes the usefulness of monoclonal antibodies in the characterization and localization of neurotransmitters such as Substance P, a peptide clearly associated with the transmission of primary sensory information in the spinal cord. The article discloses producing monoclonal antibodies from hybrid myelomas (hybridomas), their use in conventional radioimmunoassay techniques, and the benefits from doing so which flow from the ability to derive permanent cell lines capable of continuous production of highly specific antibodies.

The district court found that the examiner twice rejected all of the claims of the '110 patent based on Cuello alone or in combination with the Jeong, Piasio, and Schurr references which disclose various sandwich assays using polyclonal antibodies. The court also found that the examiner allowed the claims after they were amended to include the 10 ^{8}affinity limitation and after Richard Bartholomew, a Hybritech employee, submitted an affidavit alleging the advantages of using monoclonal rather than polyclonal antibodies in sandwich assays.

Apparently based on the testimony of Monoclonal's expert witness Judith Blakemore, a named inventor of the Jeong patent, manager of antibody programs at Bio-Rad Laboratories from 1975 to 1982, and currently manager of monoclonal antibody therapeutics at Cetus Corporation, a Hybritech competitor in immunoassay diagnostics, the district court stated

that the "reasons for allowance were not well-founded because (1) the alleged advantages were expected as naturally flowing from the well-known natural characteristics of monoclonal antibodies . . .; (2) . . . were not significant . . .; or (3) were at best minor," although they were "argued to the examiner as if they were" important. These were Monoclonal's words from its pretrial submission adopted by the court.

6. *The References That "Predicted" the Use of Monoclonal Antibodies in Immunoassays*

The district court stated, again in Monoclonal's words, that "it is of the utmost importance" that the advantages of monoclonal antibodies were "predicted by a number of authorities," eight to be exact, not important enough to list here, after the Kohler and Milstein discovery and after monoclonal antibodies became available.

B. *The Claimed Subject Matter of the '110 Patent*

Hybritech argues that the district court's determination that there is no credible evidence of conception or reduction to practice of the '110 invention before May 1980 is error because Dr. David's laboratory notebooks, Nos. 21 and 24, clearly show successful sandwich assays using monoclonal antibodies in August, September, and October of 1979. At the least, argues

Hybritech, the invention was conceived in January of 1979, long before Drs. Ruoslahti, Engvall, and Uotila began work on a sandwich assay using monoclonal antibodies, and diligence was thereafter exercised until constructive reduction to practice occurred by the filing of the '110 patent application on August 4, 1980.

Dr. David and Greene testified that pages 2118 to 2122 of Dr. David's notebook, dated January 4, 1979, and witnessed January 30, 1979, disclose the generic conception of the invention in the context of the physical support structure used to carry out a sandwich assay, and Dr. David testified on redirect that (1) Page 1128 of notebook 21, dated May 27, 1979, recorded an early attempt at a sandwich assay that failed, (2) on August 3, 1979, as recorded at page 1166, a sandwich assay using monoclonal antibody 068 attached to a solid carrier, a radio-labelled 068 antibody, and a hepatitis antigen from an Abbott Labs polyclonal competitive assay kit was successfully performed, and (3) a sandwich assay using a bound 259 antibody, a radio-labelled 068 antibody, and a hepatitis antigen was successfully performed on September 21, 1979. Hybritech also urges that work in October 1979 directed to determining whether certain monoclonal antibodies were recognizing the same or different determinants, was a reduction to practice.

Monoclonal points out that these notebook pages do not expressly state that monoclonal antibodies of 10 ^{8}liters/mole affinity were used in a sandwich assay and that the May, August, and September notebook entries were not witnessed until about the time Dr. Adams, experienced in patent matters, joined Hybritech and advised its researchers on properly recording laboratory work. They therefore claim that actual reduction to practice was not shown before May 1980.

OPINION

I. *Review Under Rule 52(a) Fed. R. Civ. P.*

Rule 52(a) "ensures care in the preparation of an opinion . . . and provides appellate courts with the benefit of the District Court's insights into a case," *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309 318, 227 USPQ 766, 772 (Fed. Cir. 1985) (Harvey, Senior District Judge, concurring) by requiring a district court to "find the facts specially and state separately its conclusions of law thereon." With the exception of the first eight paragraphs, the first half of the district court's opinion here is Monoclonal's *pretrial* brief and the last three pages of the opinion are Monoclonal's *pretrial* findings of fact and conclusions of law. The district court adopted the above documents virtually verbatim, with the exception of portions of each concerning inequitable conduct and noninfringement, apparently without inviting a response from Hybritech, resulting in a repetitious (as the district court admitted in the opinion), sometimes internally inconsistent, and hard to follow opinion that presents us with a difficult task in gleaning the basis for many of the conclusions. For some of the findings, submitted before trial, no supporting evidence was introduced at trial.

The Supreme Court, in *Anderson v. City of Bessemer City, N.C.*, 105 S.Ct. 1504 (1985), strongly criticized the practice of "verbatim adoption of findings of fact prepared by prevailing parties, particularly when those findings have taken the form of conclusory statements

unsupported by citation to the record." *Anderson,* supra at 1511. This court also has cautioned against the adoption of findings, especially when proposed by a party before trial, as here, and stated that the likelihood of clear error in those findings increases in such a situation. *Lindemann Maschinenfabrik v. American Hoist and Derrick,* 730 F.2d 1452, 1457, 221 USPQ 481, 485 (Fed. Cir. 1984).

Notwithstanding our misgivings about whether the findings in this case, prepared before any evidence was introduced, satisfy the objectives of Rule 52(a) -- a carefully prepared opinion providing the reviewing court with the benefit of the district court's *reasoned insights* into the case -- those findings are the district court's and may be reversed only if clearly erroneous. *See Anderson,* supra, at 1511; *Lindemann,* 730 F.2d at 1457, 221 USPQ at 485.

"A finding is clearly erroneous when, although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. United States Gypsum Co.,* 333 U.S. 364, 395 (1948). "This standard plainly does not entitle a reviewing court to reverse the finding of the trier of fact simply because it is convinced that it would have decided the case differently." *Anderson,* supra, at 1511. In other words, "if the district court's account of the evidence is plausible in light of the record viewed in its entirety" or "where there are two permissible views of the evidence," the factfinder cannot be clearly erroneous. *Anderson,* supra, at 1511 (quoting *United States v. Yellow Cab Co.,* 338 U.S. 338, 342 (1949)). This is so, stated the Court in dictum, *see Anderson,* supra, at 1516 (Blackmun, J., concurring), even when the district court's findings rest on physical or documentary evidence or inferences from other facts and not on credibility determinations. *See also* Rule 52(a) Fed. R. Civ. P. (as amended Aug. 1, 1985). If the latter are involved, "Rule 52 demands even greater deference to the trial court's findings" but a trial judge may not "insulate his findings from review by denominating them credibility determinations"; if documents or objective evidence contradict the witness' story, clear error may be found even in a finding purportedly based on a credibility determination. *Anderson,* supra, at 1512-13. We proceed in light of all these principles.

II. *Presumption of Validity*

Under 35 USC 282, a patent is presumed valid, and the one attacking validity has the burden of proving invalidity by clear and convincing evidence. *See, e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc.,* 725 F.2d 1350, 1360, 220 USPQ 763, 770 (Fed. Cir. 1984). Notwithstanding that the introduction of prior art not before the examiner may facilitate the challenger's meeting the burden of proof on invalidity, the presumption remains intact and on the challenger throughout the litigation, and the clear and convincing standard does not change. *See, e.g., Jervis B. Webb Co. v. Southern Systems, Inc.,* 742 F.2d 1388, 1392 & n.4, 222 USPQ 943 , 945 & n.4 (Fed. Cir. 1984). The only indication that the district court recognized the presumption of validity and its proper application was its statement that "[t]he key issue in this case is whether the defendant has overcome the presumption of nonobviousness." That statement,

however, speaks only part of the truth; the presumption of validity goes to validity of the patent in relation to the patent statute *as* a *whole,* not just to nonobviousness under Section 103.

III. *Prior Invention of Another, 35 USC 102(g)*

Section 102(g) states that a person shall be entitled to a patent unless "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." Section 102(g) "relates to prior inventorship by another in this country" and "retains the rules governing the determination of priority of invention . . . . " *Kimberly-Clark Corp. v. Johnson & Johnson,* 745 F.2d 1437, 1444, 223 USPQ 603, 606 (Fed. Cir. 1984) (quoting P.J. Federico, *Commentary on the New Patent Act,* 35 USCA page 1, at 19 (1954)). Section 102(g) says: "In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other."

Reduction to practice, and conception as well, is a legal determination subject to review free of the clearly erroneous standard. *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd,* 731 F.2d 831, 837, 221 USPQ 561, 565-66 (Fed. Cir. 1984); *D.L. Auld Co. v. Chroma Graphics Corp.,* 714 F.2d 1144, 1151, 219 USPQ 13, 18 (Fed. Cir. 1983). Findings of fact supporting that legal conclusion, are, of course, reviewed under the clearly erroneous standard.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." 1 *Robinson On Patents* 532 (1890); *Coleman v. Dines,* 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985). Actual reduction to practice requires that the claimed invention work for its intended purpose, *see, e.g., Great Northern Corp. v. Davis Core & Pad Co.,* 782 F.2d 159, 165, 228 USPQ 356, 358, (Fed. Cir. 1986), and, as has long been the law, constructive reduction to practice occurs when a patent application on the claimed invention is filed. *Weil v. Fritz,* 572 F.2d 856, 865 n.16,

196 USPQ 600 , 608 n.16 (CCPA 1978) (citing with approval *Automatic Weighing Machine Co. v. Pneumatic Scale Corp.,* 166 F. 288 (1st Cir. 1909)).

[1] After a review of the record in its entirety, including the numerous corroborating Hybritech laboratory notebooks, internal documents, and pertinent testimony, we hold clearly erroneous the district court's finding that there is no clear or corroborated evidence "with regard to when before May 1980, the idea of actually using monoclonals in sandwich assays" was conceived or, more properly, of when the *claimed invention* was conceived, and therefore reverse the court's holding, as a matter of law, that Hybritech's inventors did not conceive the claimed invention before May 1980.

Hybritech's claim of conception, generally, is evidenced by the sometimes sparsely

documented work of a start-up company whose first small advances evolved into the myriad activities of a mature company with efforts directed toward developing the claimed invention by first employing the Kohler and Milstein technology to produce the necessary monoclonal antibodies and using those antibodies in diagnostic sandwich assay kits. There is no doubt that exploiting monoclonal antibodies for use in sandwich assays was one of the major objectives of Hybritech. In a letter to Pharmacia Fine Chemicals dated April 26, 1979, Greene, in responding to Pharmacia's interest in Hybritech's products, outlined the latter's "efforts to bring the exciting new hybridoma technology into routine medical use" and its exploration of "several intriguing concepts for which monoclonals may open up new immunodiagnostic techniques heretofore infeasible with animal serums." Although company minutes in early 1979 contain little about the claimed subject matter and some of the discussions thereon, such as Greene's and Dr. Adams' conversation about monoclonal sandwich assays when the former was trying to woo Dr. Adams to join Hybritech were unrecorded, the Hybritech laboratory notebooks and the nature of Hybritech's research program fully corroborate the testimonial evidence of conception and thus clearly support our holding that Hybritech conceived the claimed invention before LJCRF.

Dr. David's January 1979 notebook describes, in detail, as explained by Greene and Dr. David at trial, a nylon apparatus that undoubtedly could be used for performing a sandwich assay using monoclonal antibodies, although Dr. David testified on cross-examination that at that time Hybritech had not yet developed any monoclonal antibodies, including attaching one of the reagents to a solid carrier ring, contacting that ring with a fluid sample in a microtiter plate well, adding a labelled reagent to the well after rinsing, and then "counting" or measuring the amount of either the labelled or unlabelled reagent after a prescribed time and second rinsing. The notebook then describes the procedure for detecting an antibody "(a-x)" to an antigen "(x)" complete with diagrams and text, both illuminated by Dr. David at trial. The notebook further states, "Alternatively, if one wished to quantitate an antigen, y, the identical procedure would be followed, except that reagents would be reversed, i.e. the reaction would be:" and there follows a clear illustration of an antibody attached to a solid carrier reacting with an antigen to form a complex, and that complex reacting with a second labelled antibody. The notebook was signed by Dr. David on January 4, 1979, and witnessed and signed on January 30 of the same year by Dr. Curry, the first cell biologist hired at Hybritech to set up the hybridoma production program.

Dr. David testified on direct that monoclonal antibodies were developed in the following months: antigens were purchased from outside sources and purified before being injected into mice; the spleen cells from those mice were fused with myelomas; and the resultant hybridomas were separated into well plates for development, and a radioimmunoassay procedure was carried out to determine the affinity of the antibodies.

The May 1979 failed sandwich assay, witnessed in May 1980, corroborates Dr. David's testimony that a polyclonal antibody bound to a solid carrier and a labelled monoclonal antibody were used in a sandwich assay with an antigen from Abbott Labs' Ausria polyclonal diagnostic kit for hepatitis. No binding was detected.

Dr. David testified about the experiment documented in the August 1979 notebook, a

sandwich assay with a hepatitis antigen from an Abbott Labs Ausria kit with two Hybritech 068 monoclonal antibodies, one attached to a solid carrier bead and the other labelled; the purpose of the experiment was to quantitate the antigen. The notebook corroborates Dr. David's testimony that the test was positive and lists the counts per minute of the labelled antibody. Defendant Monoclonal's expert Ciotti testified about this experiment:

> Also, of course, it is limited to -- it is limited to hepatitis antigen. And without a generic conception, it would just be merely a -- if it did work for its intended purpose -- which I would assume for purposes of discussion -- it *would be a reduction to practice of one embodiment.* And without a corresponding generic conception, I don't think it would be held to be the making of the invention in

> terms of, for instance, in claim 19. [Emphasis ours.]

Dr. David further testified that the September 21, 1979, record in David's notebook, witnessed months later, shows a reverse sandwich assay using a bound 259 monoclonal antibody and a labelled 068 monoclonal antibody with a hepatitis antigen with results confirmed by a dose response curve. 2 Hybritech further alleges that a laboratory notebook page dated October 1979 is a reduction to practice of the claimed invention but fails to cite any related testimony or other evidence in support thereof.

Finally, the record shows that the claimed affinity limitation "of at least about 10^8liters/mole" was determined and appreciated during the course of the development of the claimed subject matter. Dr. David and Dr. Adams separately testified that the screening procedures used by Hybritech ensured that only monoclonal antibodies having at least 10^8liters/mole affinity would be used in assays. An October 1979 internal memorandum from Greene to the staff states "To improve comparisons we will express all affinities to the base ten to the eighth which represents the lower end of the useable range."

We are left with the definite and firm conviction that a mistake has been committed because the district court's account of the evidence that "there was no credible evidence of conception before May 1980" is insupportable. There is such evidence. The laboratory notebooks, alone, are enough to show clear error in the findings that underlie the holding that the invention was not conceived before May 1980. That some of the notebooks were not witnessed until a few months to one year after their writing does not make them incredible or necessarily of little corroborative value. Admittedly, Hybritech was a young, growing company in 1979 that failed to have witnesses sign the inventors' notebooks contemporaneously with their writing. Under a reasoned analysis and evaluation of all pertinent evidence, however, we cannot ignore that Hybritech, within a reasonable time thereafter, prudently had researchers other than those who performed the particular experiments witness the notebooks in response to Tom Adams' advice. The notebooks clearly show facts underlying and contemporaneous with conception of the claimed invention and in conjunction with the testimony of Dr. David and Greene, and others, are

altogether legally adequate documentary evidence, under the law pertaining to conception, of the formation in the minds of the inventors of a definite and permanent idea of the complete and operative invention as it was thereafter applied in practice. We thus are not moved by Monoclonal's argument that the findings of fact underlying conception are based on credibility determinations and are more sacrosanct than usual. *See Anderson,* supra, at 1512-13.

1. *LJCRF Is Not Prior Art*

Hybritech laboratory notebooks and the uncontradicted testimony of Dr. David and Mr. Greene show that development of the claimed invention proceeded diligently through the rest of 1979 and 1980, there being absolutely no evidence of record nor even argument by Monoclonal that Hybritech was not diligent in its efforts to reduce to practice the claimed invention during the period January 1979 to the '110 application filing date of August 4, 1980. We therefore hold as a matter of law that Hybritech's conception, which was before LJCRF conceived the claimed invention, coupled by diligence to its constructive reduction to practice by the filing of the '110 application, entitle Hybritech to priority over LJCRF. *See* 35 USC 102(g). The work of LJCRF is therefore not prior art.

We also note that there is inadequate factual basis for the district court's holding that LJCRF reduced the claimed invention to practice as early as November 1979 because the only evidence that corroborates the testimony of Ruoslahti, Uotila, and Engvall is the note from Ruoslahti to Uotila, see section A, 2, supra, which indisputably is not the claimed invention, and the *one* curve from *one* graph from only one page, 43D, of the six Uotila notebooks. After a reasoned examination, analysis, and evaluation of this pertinent evidence we conclude that it falls far short of showing the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice," *see Coleman,* 754 F.2d at 359, 224 USPQ at 862, and therefore is legally inadequate to support even a holding of *conception* of the claimed invention by LJCRF personnel in 1979.

(1) It is undisputed that page 43D was not signed, witnesed, or dated; (2) the deposition testimony of Uotila was that she could not remember the procedure used to arrive at the dose-response curve on page 43D and there was not enough information in her notebook to refresh her memory; (3) the testimony of

Ruoslahti was that he could find *no* data in the notebook supporting that graph, none of the *later* graphs shown there represented successful assays and that "especially after this was done, we ran into more severe problems. And it took us a while to do away with the problems;" (4) Ruoslahti also testified that they never determined, in 1979, the affinities of the monoclonal antibodies they used, and that the title of page 43D had been altered at some point -- the word "inhibition" had been crossed out and "sandwich" written in; and (5) the testimony of Engvall was that there was nothing about the shape of those curves which indicates that they were sandwich assays. We also note, as evidence bearing upon the credibility of Ruoslahti's testimony (that LJCRF actually

reduced the claimed invention to practice in 1979), that when LJCRF attempted to provoke an interference in the PTO with Hybritech based on the U.S. filing of an application that was the counterpart to a Swedish application disclosing similar subject matter, LJCRF could not demonstrate even a *prima facie* reduction to practice prior to Hybritech's August 4, 1980, filing date. During that proceeding, the earliest dates Ruoslahti set down on paper to support conception and reduction to practice were in 1980.

2. *The Work of Oi/Herzenberg Is Not the Claimed Invention*

[2] It is axiomatic that for prior art to anticipate under §102 it has to meet every element of the claimed invention, and that such a determination is one of fact. *See, e.g., Lindemann,* supra, 730 F.2d at 1458, 221 USPQ at 485; *Great Northern Corp. v. Davis Core & Pad Co.,* 782 F.2d 159, 165, 228 USPQ 356, 358 (Fed. Cir. 1986). Section 102(g) upon which the district court relied is one type of "anticipation," i.e., prior invention by another of the same invention. Drs. Oi and Herzenberg testified that their work did not involve detecting the presence of or quantitating antigen but a determination of the number and location of epitopes on a *known* quantity of antigen. Although this work did involve a sandwich assay to the extent that an antigen was sandwiched between two monoclonal antibodies, it is clear that the similarity between that work and the claimed invention goes no further. Furthermore, both doctors testified that they did not know the affinities of the antibodies that were used in their mapping work and in fact never calculated them. Ciotti, Monoclonal's expert, testified that the 10^{8}affinity limitation cannot be found anywhere in the Oi/Herzenberg work. Again we are left with a definite and firm conviction that a mistake was made because that work does not meet every element of the claimed invention. The district court's finding to the contrary is clearly erroneous.

We note that the district court, in also holding the patent invalid under §103, next considered, combined the Oi/Herzenberg work with the Frankel reference, one justifiable inference therefrom being that the court recognized that Frankel discloses a claim *element* that Oi/Herzenberg does not, namely, at least about 10^{8}liters/mole affinity.

IV. *Obviousness, 35 USC 103*

A section 103 obviousness determination -- whether the claimed invention *would have been* (not "would be" as the court repeatedly stated because Monoclonal's pretrial papers used that improper language) obvious at the time the invention was made is reviewed free of the clearly erroneous standard although the underlying factual inquiries -- scope and content of the prior art, level of ordinary skill in the art, 3 and differences between the prior art and the claimed invention -- integral parts of the subjective determination involved in §103, are reviewed under that standard. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered *before* a conclusion on obviousness is reached and is not merely "icing on the cake," as the district court stated at trial. *See Lindemann,* supra, 730 F.2d at 1461, 221 USPQ at 488; *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Kansas Jack, Inc. v. Kuhn,* 719 F.2d 1144, 219 USPQ 856 (Fed. Cir. 1983); *W.L. Gore & Associates v. Garlock Inc.,* 721 F.2d 1540, 220 USPQ 303, 314 (Fed. Cir. 1983).

1. *The Eight Articles "Predicting" Widespread Use of Monoclonal Antibodies*

Before discussing the more pertinent references in this case -- the Oi/Herzenberg and Frankel works -- we cull the other prior art references relied on by the trial court.

[3] First, the latest four of the eight articles that the court stated were of the "utmost importance" because they "predicted" that the breakthrough in production of monoclonal antibodies by Kohler and Milstein would lead to widespread use of monoclonal antibodies in

immunoassays are neither 102(a)/103 nor 102(b)/103 prior art because they are dated between late 1979 and March 6, 1980, well after the date of conception and within one year of the filing date of the '110 patent.

The earliest four of the eight articles, on the other hand, although clearly prior art, discuss *production* of monoclonal antibodies -- admittedly old after Kohler and Milstein showed how to produce them -- but none discloses sandwich assays. At *most,* these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished. To the extent the district court relied upon these references to establish that it would have been *obvious to try* monoclonal antibodies of 10 ^{8}liters/mole affinity in a sandwich immunoassay that detects the presence of or quantitates antigen, the court was in error. *See Jones v. Hardy,* 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984) ("Obvious to try" is improper consideration in adjudicating obviousness issue). 4

2. *The Kohler and Milstein Work, the Cuello Article and the Jeong, Piasio, and Schurr Patents Considered by the Examiner*

The district court's finding that Kohler and Milstein developed a method for producing monoclonal antibodies in vitro is correct, but that finding proves no more; although it made possible all later work in that it paved the way for a supply of monoclonal antibodies, it indisputably does not suggest using monoclonal antibodies in a sandwich assay in accordance with the invention claimed in the '110 patent.

The Cuello reference discloses monoclonal antibodies but not in a sandwich assay. The competitive assay in Cuello, moreover, uses only one monoclonal antibody and thus in no way suggests the claimed invention wherein a ternary complex of two monoclonal antibodies and an antigen form a sandwich. Furthermore, the court did not explain how this art, by itself or in combination with any of the other art, suggests the claimed subject matter and thus why that combination would have been obvious. We are of the opinion that it does not.

The district court correctly found that the use of polyclonal antibodies in sandwich assays was well known. The Jeong patent discloses the use of polyclonal antibodies in a simultaneous sandwich assay, with no suggestion that monoclonal antibodies be so used. It is prior art by

virtue of §102(e), application for the patent having been filed September 5, 1978, its effective date as a reference. The Piasio patent, disclosing a reverse sandwich assay using polyclonal antibodies, and Schurrs, disclosing a forward sandwich assay using the same, both §102(a) prior art, are likewise devoid of any suggestion that monoclonal antibodies can be used in a similar fashion.

3. *The Oi/Herzenberg Work and the Frankel Article*

Clearly, the most pertinent items of prior art not cited by the examiner are the Oi/Herzenberg work, as described in section A, 3, supra, and the Frankel article. As stated in the discussion of Prior Invention of Another (section III, 2, supra), the Oi/Herzenberg work involved mapping epitopes on a known quantity of antigen. It was not concerned with and does not disclose using monoclonal antibodies of at least 10 ^{8}liters/mole affinity. Oi and Herzenberg testified that they did not know the affinity of the antibodies used, and Ciotti testified that nowhere in that work is there mention of monoclonal antibody affinity of at least 10 ^{8}liters/mole. On this basis, we conclude that the Oi/Herzenberg work is qualitatively different than the claimed invention; the former is directed to mapping epitopes on a known quantity of antigen and the latter to determining the "presence or concentration of an antigenic substance in a sample of fluid . . . . " We disagree with Monoclonal that these are "essentially the same thing." Furthermore, it is perfectly clear that this work in no way suggests using monoclonal antibodies of the affinity claimed in the '110 patent. It is because of these differences between the Oi/Herzenberg work and the claimed invention that the fact that an antigen was sandwiched between two monoclonal antibodies in the course of Oi's and Herzenberg's work is not sufficient basis to conclude that the claimed invention would have been obvious at the time it was made to a person of ordinary skill in the art.

Likewise, a conclusion that the invention would have been obvious cannot properly be reached when the Oi/Herzenberg work is

considered in view of the Frankel article. Frankel teaches a method for rapid determination of affinity constants for monoclonal antibodies, some of which clearly have affinities of the order defined by the claims, but does not in any way suggest using two of those antibodies in a sandwich to assay an antigen by forming a ternary complex of labelled antibody, the antigenic substance, and a bound antibody wherein the presence of the antigenic substance is determined by measuring either the amount of labelled antibody bound to a solid carrier or the amount of unreacted labelled antibody. The mere existence of prior art disclosing how to measure the affinity of high affinity monoclonal antibodies is insufficient to support a holding of obviousness. Hybritech's claims define a *process* that *employs* monoclonal antibodies, and does not merely claim antibodies of high affinity. In view of the fact that the Oi/Herzenberg work is not directed to an assay as claimed and does not disclose antibodies of at least 10 ^{8}liters/mole affinity, and further that Frankel fails to suggest using such antibodies in a sandwich assay, the Frankel article does not compensate for the substantial difference between the Oi/Herzenberg work and the

claimed subject matter, and therefore those references in combination cannot support a holding of obviousness.

4. *Objective Evidence of Nonobviousness*

[4] In one part of its opinion the court found that "the commercial success of the kits *may* well be attributed to the business expertise and acumen of the plaintiff's personnel, together with its capital base and marketing abilities" (emphasis ours) and later that "[w]here commercial success is based on the sudden availability of starting materials, in this instance the availability of monoclonal antibodies as a result of the Kohler and Milstein discovery, business acumen, marketing ability, and capital sources, no causal relationship is proven." (Citation omitted.)

i. *Commercial Success: Hybritech's Diagnostic Kits Grabbed a Substantial Market Share*

The undisputed evidence is that Hybritech's diagnostic kits had a substantial market impact. The first diagnostic kit sales occurring in mid-1981, sales increased seven million dollars in just over one year, from $6.9 million in-1983 to an estimated $14.5 million in 1984; sales in 1980 were nonexistent. Competing with products from industry giants such as Abbott Labs, Hoffman LaRoche, Becton-Dickinson, and Baxter-Travenol, Hybritech's HCG kit became the market leader with roughly twenty-five percent of the market at the expense of market shares of the other companies. Its PAP kit ranks second only to a product sold by Dupont's New England Nuclear, surpassing products from Baxter-Travenol, Abbott, and others. Hybritech's other kits, indisputably embodying the invention claimed in the '110 patent, obtained similar substantial market positions.

Although the district court did not provide its insights into why commercial success was due to business acumen and not to the merits of the claimed invention, Monoclonal urges in support that it was due to Hybritech's spending disproportionate sums on marketing, 25-30% of income. The undisputed evidence was that expenditures of *mature* companies in this field are between 17 and 32%. Furthermore, the record shows that advertising makes those in the industry -- hospitals, doctors, and clinical laboratories -- aware of the diagnostic kits but does not make these potential users buy them; the products have to work, and there is no evidence that that is not the case here or that the success was not due to the merits of the claimed sandwich assays -- clearly contrary to the district court's finding.

The trial court's finding that the "sudden availability of monoclonals" was the reason for the commercial success of Hybritech's diagnostic kits (Finding 11) is unsupported by the record and clearly erroneous. Monoclonal admits that monoclonal antibodies were available in the United States in *1978,* and the evidence clearly reflects that. Thus, at least *three years* passed between the time monoclonal antibodies were available in adequate supply and the time Hybritech began selling its kits. Especially in the fast-moving biotechnology field, as the evidence shows, that is anything but sudden availability.

ii. *Unexpected Advantages*

Hybritech points to the testimony of three witnesses skilled in the diagnostic field who state that, based on tests done in their laboratories as a result of real-world comparisons in the normal course of research, the diagnostic kits that embody the '110 invention unexpectedly solved longstanding problems. Dr. Hussa, the head of a large referral laboratory and a world-wide consultant, testified that until Hybritech introduced its kits, he and others were very skeptical and had almost exclusively used competitive assays with a radioactive tracer (RIAs). 5 In relation to an HCG Hybritech

kit, he testified that he had first thought that the Hybritech HCG kit would not give accurate results for low antigen concentrations because that condition is indicated in the Hybritech kit by a low radioactivity reading, a reading difficult to differentiate from control samples containing no antigen. He also stated that in the past, RIA kits falsely detected HCG in nonpregnant women, a condition which would indicate cancer and surgery. He stated that when he employed the Hybritech HCG kit in such instances it demonstrated, correctly and absent any difficulty interpreting the data, that no HCG was present.

Dr. Blethen, an M.D. holding a Ph.D. in biochemistry, testified that she did not think that the Hybritech HGH kit, for detecting growth hormone in children, would offer any advantage, but she determined that it detected HGH deficiencies in children where conventional RIAs failed to do so. She also stated that the kit does not give false positive readings as do conventional RIA kits, an opinion shared by Dr. Hussa. A third witness, Dr. Herschman, who holds a master's degree in chemistry, testified that he spent years working on the development of an assay that would determine the presence of TSH (thyroid stimulating hormone) with greater sensitivity. He succeeded but discovered that the Hybritech TSH kit had the same sensitivity, the test being performed in four hours rather than the three days his kit required.

Having considered the evidence of nonobviousness required by §103 and *Graham,* supra, we hold, as a matter of law, that the claimed subject matter of the '110 patent would not have been obvious to one of ordinary skill in the art at the time the invention was made and therefore reverse the court's judgment to the contrary. The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity, *Lindemann,* 730 F.2d at 1462, 221 USPQ at 488, *as a whole. See* 35 USC 103; *Jones v. Hardy,* 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984). Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. *See generally Hodosh v. Block Drug Co,* 786 F.2d 1136, 229 USPQ 182 (Fed. Cir. 1986). 6

With respect to the objective indicia of nonobviousness, while there is evidence that marketing and financing played a role in the success of Hybritech's kits, as they do with any product, it is clear to us on the entire record that the commercial success here was due to the merits of the claimed invention. It cannot be argued on this record that Hybritech's success would have been as great and as prolonged as admittedly it has been if that success were not due to the merits of the invention. The evidence is that these kits compete successfully with numerous others for the trust of persons who have to make fast, accurate, and safe diagnoses. This is not the kind of merchandise that can be sold by advertising hyperbole.

V. *Enablement, Best Mode, and Definiteness Under §112*

The section 112 defense appears to have been an afterthought of both Monoclonal, who briefly but unsuccessfully attempts to defend this utterly baseless determination, and of the district court which adopted the defense from Monoclonal's pretrial papers apparently without knowledge of the applicable law, to highlight, as it stated at trial, that it was part of its job to see that "whoever wins wins all the way or whoever loses loses all the way." Taken as a whole, the court's comments on §112 -- split into two parts, one from Monoclonal's pretrial brief and the other from the adopted pretrial

findings and conclusions -- are internally inconsistent. The opinion states that the patent fails to disclose how (1) to make monoclonal antibodies; (2) to screen for proper monoclonal antibodies; and (3) to measure monoclonal antibody affinity and therefore the specification is nonenabling and does not satisfy the best mode requirement, and the claims are indefinite. We discuss each of these in turn.

1. *Enablement*

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive, *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), and is determined as of the filing date of the patent application, which was August 4, 1980. *See W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983). Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *Lindemann,* 730 F.2d at 1463, 221 USPQ at 489.

The record fully supports the '110 patent's statement that

> The monoclonal antibodies used for the present invention are obtained by the [hybridoma] process discussed by Milstein and Kohler. . . . The details of this process are well known and not repeated here.

The district court itself stated that the "method for producing monoclonal antibodies in vitro was well known prior to the alleged invention of the '110 patent," and used the "sudden availability of monoclonal antibodies" produced by the Kohler and Milstein discovery to support, albeit erroneously, its finding of a lack of nexus between the merits of the claimed invention and its commercial success. The court then about-faced and held the '110 patent deficient because it fails to teach how to make monoclonal antibodies.

With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those. At trial, Monoclonal's counsel stated "it is a procedure that was known in '78." In similar fashion, the district court held that the claimed subject matter would have been obvious in part because the "existence of monoclonal antibodies *having the affinity constants claimed in the patent was well known* prior to the alleged invention . . . ." [Emphasis ours.] Furthermore, there was not a shred of evidence that undue experimentation was required by those skilled in the art to practice the invention. We hold as a matter of law that the '110 patent disclosure is enabling.

2. *Best Mode*

"The specification . . . shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 USC 112. Because not complying with the best mode requirement amounts to concealing the preferred mode contemplated by the applicant at the time of filing, in order to find that the best mode requirement is not satisfied, it must be shown that the applicant knew of and concealed a better mode than he disclosed. *DeGeorge v. Bernier,* 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985) (quoting with approval *In re Sherwood,* 613 F.2d 809, 204 USPQ 537 (CCPA 1980)). The only evidence even colorably relating to concealment is testimony by various Hybritech employees that sophisticated, competent people perform the screening and that the screening process is labor-intensive and time-consuming. It is not plausible that this evidence amounts to proof of concealment of a best mode for screening or producing monoclonal antibodies for use in the claimed '110 process, and therefore we are of the firm conviction that the district court's finding that the best mode requirement was not satisfied is clearly erroneous.

3. *Indefiniteness*

[5] The basis of the district court's holding that the claims are indefinite is that "they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency." (Conclusion 6.) Even if the district court's finding in support of this holding -- that "there is no standard set of experimental conditions which are used to estimate affinities" -- is accurate, under the law pertaining to indefiniteness -- "if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," *Shatterproof Glass Corp. v. Libbey Owens Ford Co.,* 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) -- the claims clearly are definite. The evidence of record indisputably

shows that calculating affinity was known in the art at the time of filing, and

notwithstanding the fact that those calculations are not precise, or "standard," the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more.

VI. *Motions*

Monoclonal's motion to strike Appendices A and B of Hybritech's reply brief as being beyond the page limit applicable to reply briefs is granted as to Appendix A but denied as to Appendix B, the latter having been helpful in culling the often non-supportive citations to the record by Monoclonal.

Hybritech's motion to supplement the record with a Monoclonal advertisement not considered at trial is denied. Any adverse impact that the disposition of these two motions has upon either party is more than outweighed by this court's patience with the seemingly endless flow of post-argument argumentative papers.

VII. *Conclusion*

The judgment of the district court holding the patent in suit invalid is *reversed* in all respects, and the case is *remanded* for a determination of the issue of infringement which the court held was moot.

REVERSED AND REMANDED

Footnotes

Footnote 1. With respect to obviousness, one portion of the district court's opinion apparently relies on all of the above listed references, (1)-(5), for the obviousness holding while a later portion entitled "CONCLUSIONS OF LAW" relies on only the Oi/Herzenberg and Frankel articles. Furthermore, the district court did not state that the LJCRF work was considered for purposes of §103, although we recognize that §102(g) prior art can be used for §103.

Footnote 2. A dose response curve is antigen concentration plotted against the signal produced by labelled antibody in an immunoassay. The signal increases with increasing antigen concentration in a successful assay but at some point decreases when the antigen concentration becomes too

high.

Footnote 3. Although the district court failed expressly to find the level of ordinary skill in the art at the time the invention was made, it did make reference to "[p]eople working in immunology aware of the Kohler and Milstein discovery" which we deem an accurate finding for the purposes of that portion of the *Graham* factual inquiries.

Footnote 4. Finding 10, which states that the invention was contemporaneously developed and disclosed in at least five publications and patent applications not listed above *and dated well after the filing date of the '110 patent but before its issuance* is irrelevant for purposes of the hypothesis based on the three factual inquiries required by §103 as interpreted by *Graham v. John Deere,* 383 U.S. 1, 148 USPQ 459 (1966) because obviousness must be determined as of the time the invention was made. Additionally, they are of little probative value in this case because they are dated December 1981 at the earliest, more than a year after the August 4, 1980, filing date here and roughly two years after conception occurred. Furthermore, simultaneous development may or may not be indicative of obviousness, the latter being the case here for the above reasons and because the other evidence of nonobviousness is adequate, such occurrences having been provided for in 35 USC 135. *Lindemann,* supra, 730 F.2d at 1460-61, 221 USPQ at 487; *Environmental Designs, Ltd. v. Union Oil Co. of California,* 713 F.2d 693, 698 n.7, 218 USPQ 865 , 869 n.7 (Fed. Cir. 1983)

Footnote 5. Monoclonal's expert Blakemore testified that of 425 assays on the market in 1979 less than 1% were sandwich assays. Today, sandwich assays constitute the majority of all assays sold.

The record also shows that Blakemore, who testified extensively for Monoclonal that the claimed invention would have been obvious, never used monoclonal antibodies in sandwich assays at Cetus before 1980. Additionally, she did not even mention them in the Jeong patent, of which she was a coinventor, which issued January 13, 1981, long after the beginning of Hybritech's work in this area in 1979.

Footnote 6. It bears repeating that it is crucial that counsel set forth the law accurately. More particularly, it is the duty of counsel to impart to the judge that the obviousness question properly is whether the *claimed* invention *as a whole would have been* obvious to one of *ordinary* skill in the art *at the time the invention was made,* and that the district court must *expressly* make the three factual determinations required by *Graham* and consider objective evidence of obviousness *before* the legal conclusion of obviousness vel non is made. Submitting to the court language like "any differences . . . would have been obvious," as was done here, violates the axiom that the question is not whether the differences would have been obvious but the claimed invention *as a whole.* Furthermore, arguing that "it would be obvious" rather than that it would *have been* obvious shifts the court's focus to the wrong period of time, namely to a time long after the invention was made, in which, more likely than not, the prior art and the level of ordinary skill in the art are more advanced. *See* 35 USC 103.

- End of Case -

While amendments to the specification and claims involving new matter are ordinarily entered, such matter is required to be canceled from the descriptive portion of the specification, and the claims affected are rejected under 35 U.S.C. 112, first paragraph.

When new matter is introduced into the specification, the amendment should be objected to under 35 U.S.C. 132 (35 U.S.C. 251 if a reissue application) and a requirement made to cancel the new matter. The subject matter which is considered to be new matter must be clearly identified by the examiner. If the new matter has been entered into the claims or affects the scope of the claims, the claims affected should be rejected under 35 U.S.C. 112, first paragraph, because the new matter is not described in the application as originally filed.

A "new matter" amendment of the drawing is ordinarily not entered; neither is an additional or substitute sheet containing "new matter" even though stamped APPROVED by the Draftsman and provisionally entered by the examining group technical support staff. See MPEP § 608.02(h).

The examiner's holding of new matter may be petitionable or appealable. See MPEP § 608.04(c).

For new matter in reissue application, see MPEP § 1411.02. For new matter in substitute specification, see MPEP § 608.01(q).

Note: No amendment is permitted in a provisional application after it receives a filing date.

608.04(a) Matter Not in Original Specification, Claims, or Drawings

Matter not in the original specification, claims, or drawings is usually new matter. Depending on circumstances such as the adequacy of the original disclosure, the addition of inherent characteristics such as chemical or physical properties, a new structural formula or a new use may be new matter. See *Ex parte Vander Wal,* 109 USPQ 119, 1956 C.D. 11, 705 O.G. 5 (Bd. App. 1955) (physical properties), *Ex parte Fox*, 128 USPQ 157, 1960 C.D. 28, 761 O.G. 906 (Bd. App. 1957) (new formula) and *Ex parte Ayers,* 108 USPQ 444 (Bd. App. 1955) (new use). For rejection of claim involving new matter, see MPEP § 706.03(o).

For completeness of disclosure, see MPEP § 608.01(p). For trademarks and tradenames, see MPEP § 608.01(v).

608.04(b) New Matter by Preliminary Amendment

An amendment is sometimes filed along with the filing of the application. Such amendment does not enjoy the status as part of the original disclosure in an application filed under 37 CFR 1.53(b) accompanied by a signed oath or declaration unless it is referred to in the oath or declaration filed therewith. Once an oath or declaration is submitted in an application filed under 37 CFR 1.53(b) identifying the papers which the inventor(s) has "reviewed and understands" as required by 37 CFR 1.63, the original disclosure of the application is defined and cannot be altered merely by filing of a subsequent oath or declaration referring to different papers. Where a 37 CFR 1.53(b) application is filed without a signed oath or declaration and such application is accompanied by an amendment, that amendment is considered a part of the original disclosure. The subsequently filed oath or declaration must refer to both the application and the amendment. See MPEP § 714.09. If the original executed oath or declaration filed on the filing date of the application fails to refer to the preliminary amendment which was included with the application papers on filing, the preliminary amendment will not be considered part of the original disclosure. Any request to treat the preliminary amendment as a part of the original disclosure is by way of petition under 37 CFR 1.182, requesting that the original oath or declaration be disregarded and that the application be treated as an application filed without an executed oath or declaration under 37 CFR 1.53(f). Any such petition must be timely filed and be accompanied by a newly executed oath or declaration (which identifies the application and refers to the preliminary amendment), the surcharge set forth in 37 CFR 1.16(e), and the $130.00 petition fee.

An amendment which adds additional disclosure filed with a request for a continuation-in-part application filed prior to December 1, 1997 under former 37 CFR 1.62 is automatically considered a part of the original disclosure of the application by virtue of the rule. Therefore, the oath or declaration filed in such an application must identify the amendment adding additional disclosure as one of the papers which the inventor(s) has "reviewed and understands" in order to comply with 37 CFR 1.63. If the original oath or declaration submitted in a continuation-in-part application filed prior to December 1, 1997 under former 37 CFR 1.62

does not contain a reference to the amendment filed with the request for an application under former 37 CFR 1.62, the examiner must require a supplemental oath or declaration referring to the amendment.

608.04(c) Review of Examiner's Holding of New Matter

Where the new matter is confined to amendments to the specification, review of the examiner's requirement for cancelation is by way of petition. But where the alleged new matter is introduced into or affects the claims, thus necessitating their rejection on this ground, the question becomes an appealable one, and should not be considered on petition even though that new matter has been introduced into the specification also. 37 CFR 1.181 and 37 CFR 1.191 afford the explanation of this seemingly inconsistent practice as affecting new matter in the specification.

608.05 Deposit of Computer Program Listings

37 CFR 1.96. Submission of computer program listings.

(a) *General.* Descriptions of the operation and general content of computer program listings should appear in the description portion of the specification. A computer program listing for the purpose of this section is defined as a printout that lists in appropriate sequence the instructions, routines, and other contents of a program for a computer. The program listing may be either in machine or machine-independent (object or source) language which will cause a computer to perform a desired procedure or task such as solve a problem, regulate the flow of work in a computer, or control or monitor events. Computer program listings may be submitted in patent applications as set forth in paragraphs (b) and (c) of this section.

(b) *Material which will be printed in the patent.* If the computer program listing is contained on ten printout pages or less, it must be submitted either as drawings or as part of the specification.

(1) *Drawings.* If the listing is submitted as drawings, it must be submitted in the manner and complying with the requirements for drawings as provided in § 1.84. At least one figure numeral is required on each sheet of drawing.

(2) *Specification.* (i) If the listing is submitted as part of the specification, it must be submitted in accordance with the provisions of § 1.52, at the end of the description but before the claims.

(ii) Any listing submitted as part of the specification must be direct printouts (i.e., not copies) from the computer's printer with dark solid black letters not less than 0.21 cm. high, on white, unshaded and unlined paper, and the sheets should be submitted in a protective cover. Any amendments must be made by way of submission of a substitute sheet.

(c) *As an appendix which will not be printed.* If a computer program listing printout is eleven or more pages long, applicants must submit such listing in the form of microfiche, referred to in the specification (see § 1.77(a)(6)). Such microfiche filed with a patent application is to be referred to as a "microfiche appendix." The "microfiche appendix" will not be part of the printed patent. Reference in the application to the "microfiche appendix" must be made at the beginning of the specification at the location indicated in § 1.77(a)(6). Any amendments thereto must be made by way of revised microfiche.

(1) *Availability of appendix.* Such computer program listings on microfiche will be available to the public for inspection, and microfiche copies thereof will be available for purchase with the file wrapper and contents, after a patent based on such application is granted or the application is otherwise made publicly available.

(2) *Submission requirements.* Except as modified or clarified in this paragraph (c)(2), computer-generated information submitted as a "microfiche appendix" to an application shall be in accordance with the standards set forth in 36 CFR Part 1230 (Micrographics).

(i) Film submitted shall be a first generation (camera film) negative appearing microfiche (with emulsion on the back side of the film when viewed with the images right reading).

(ii) Reduction ratio of microfiche submitted should be 24:1 or a similar ratio where variation from said ratio is required in order to fit the documents into the image area of the microfiche format used.

(iii) At least the left-most third (50 mm. x 12 mm.) of the header or title area of each microfiche submitted shall be clear or positive appearing so that the Patent and Trademark Office can apply an application number and filing date thereto in an eye-readable form. The middle portion of the header shall be used by applicant to apply an eye-readable application identification such as the title and/or the first inventor's name. The attorney's docket number may be included. The final right-hand portion of the microfiche shall contain sequence information for the microfiche, such as 1 of 4, 2 of 4, etc.

(iv) Additional requirements which apply specifically to microfiche of filmed paper copy:

(A) The first frame of each microfiche submitted shall contain a test target.

(B) The second frame of each microfiche submitted must contain a fully descriptive title and the inventor's name as filed.

(C) The pages or lines appearing on the microfiche frames should be consecutively numbered.

(D) Pagination of the microfiche frames shall be from left to right and from top to bottom.

(E) At a reduction of 24:1, resolution of the original microfilm shall be at least 120 lines per mm. (5.0 target).

(F) An index, when included, should appear in the last frame (lower right hand corner when data is right-reading) of each microfiche.

(v) Microfiche generated by Computer Output Microfilm.

(A) The first frame of each microfiche submitted should contain a resolution test frame.

(B) The second frame of each microfiche submitted must contain a fully descriptive title and the inventor's name as filed.

(C) The pages or lines appearing on the microfiche frames should be consecutively numbered.

(D) It is preferred that pagination of the microfiche frames be from left to right and top to bottom but the alternative, i.e., from top to bottom and from left to right, is also acceptable.

(E) An index, when included, should appear on the last frame (lower right hand corner when data is right reading) of each microfiche.

the other ingredients. Thus the patent states that

> * * * It is quite likely that the silica flour reacts with clay constituents to form refractory silicates. These silicates also possess cementing properties which possibly account for the greater hot strength of mold obtained. * * *

Since silica flour is relied on for its chemical action, it would not be obvious that olivine flour, which differs materially from silica flour chemically, would form an acceptable substitute for it in Dietert's composition.

While the prior art shows that silica sand, western bentonite, and olivine are all old ingredients in molding compositions, it does not suggest the use of those ingredients in a single composition in the proportions stated in the appealed claims. Appellants' specification clearly indicates that the claimed composition has definite advantages, not only in reducing the silicosis hazard, but in improving other properties of the composition, and it was conceded by the board that "the properties of the claimed composition are superior to those of the composition disclosed in Dietert." Since appellants have produced a substantially improved composition by making an unobvious combination of ingredients, the appealed claims should have been allowed.

The decision of the Board of Appeals is *reversed.*

JACKSON, Judge, retired, recalled to participate in place of Cole, Judge, absent because of illness.

RICH, Judge, Concurring, in which JACKSON, Judge, joins.

I agree that the rejection of the claims should be reversed but my view of the prior art is this:

The Dietert reference clearly teaches a molding sand composed of silica sand, bentonite and silica flour in the proportions claimed. The first two ingredients are conventional. This reference teaches the addition of silica flour to overcome disadvantages in using cheaper and more readily available clays than bentonite, such as montmorillonite, but, far from precluding the use of bentonite, he concludes his specification by saying in effect that any clay suitable for foundry use may be used.

The British Goldschmidt patent, however, fails to suggest the substitution of olivine flour for the silica flour in the Dietert patent composition. It teaches the use of a mold body made entirely of granular olivine, from which fines in the flour category have been carefully removed, and bound with a suitable clay such as bentonite. His mold contains no silica sand at all. The fines he has removed, or fines otherwise produced and fine enough to be called flour, are then made into a slurry and painted on the mold as a facing. I do not see how this would suggest the incorporation of olivine flour in a silica sand and bentonite molding composition.

I regard the avoidance of the silicosis hazard as merely an obvious advantage attendant upon the avoidance in the foundry of materials which produce it. While this occupational hazard may have been an incentive which led to the making of the invention, I cannot see that it should be taken into account in determining patentability. Applicant has not discovered either the cause of nor a cure for silicosis. Patentability should not be predicated to any degree on the fact that olivine does not cause silicosis for the further reason that this fact is disclosed by Goldschmidt.

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44 C.C.P.A. (Patents) 820

Court of Customs and Patent Appeals

In re STEMPEL

Appl. No. 6245 Decided Feb. 21, 1957

PATENTS

1. Affidavits — Anticipating references (§ 12.3)

When domestic patent discloses, but does not claim, only a single species of invention, it cannot be used as basis of rejection of applicant's generic claims where applicant submits Rule 131 affidavit showing completion of invention of that species prior to effective date of reference.

2. Affidavits — Anticipating references (§ 12.3)

All applicant can be required to show by Rule 131 affidavit is priority with respect to so much of claimed invention as reference shows; when he has done that he has disposed of reference; it is too literal construction of Rule to hold that the invention, the completion of which must be shown by affidavit, is the invention defined in claim the applicant is asking for and, if it is generic claim, prior completion of generic invention must be shown, whether or not reference discloses generic invention.

3. Patent grant—In general (§ 50.01)

Patent statutes give to inventors the right to patent upon compliance with their provisions; neither Patent Office Rules nor interpretation placed upon them can detract from these rights.

4. Patent grant—In general (§ 50.01)

Under 35 U.S.C. 102, applicant is entitled to patent unless it is shown that one of prohibitory provisions therein, or elsewhere in statute, applies.

5. Patentability—Anticipation—In general (§ 51.201)

Patentability—Anticipation—Carrying date back of references (§ 51.203)

Reference is valid only for what it discloses; if applicant establishes priority as to that disclosure, and there is no statutory bar, it is of no effect.

6. Affidavits — Anticipating references (§ 12.3)

Patentability—Anticipation—In general (§ 51.201)

Words and phrases (§ 70.)

"Reference" is nothing more than patent or publication cited to show that all or part of invention for which patent is sought was in prior art, either more than year before filing date to which applicant is entitled, in which case it is "statutory bar" and cannot be sworn back of, or before applicant's date of invention.

7. Affidavits — Anticipating references (§ 12.3)

Patentability—Anticipation—Carrying date back of references (§ 51.203)

When reference is not a statutory bar, Rule 131 provides procedure by which applicant is permitted to show that his date of invention was earlier than date of reference; Rule must be construed in accordance with rights given to inventors by statute; this excludes construction permitting further use of reference as ground of rejection after all pertinent subject matter in it has been antedated to satisfaction of Patent Office.

Particular patents—Benzenes

Stempel, Nuclear Disubstituted Isopropenyl Benzenes, claims 1 to 4, 12, 14, and 15 of application allowed.

Appeal from Board of Appeals of the Patent Office.

Application for patent of Guido H. Stempel, Jr., Serial No. 145,590; Patent Office Division 31. From decision rejecting claims 1 to 4, 12, 14, and 15, applicant appeals. Reversed.

FRANK S. GREENE (MCCOY, GREENE & TE GROTENHUIS and WILLIAM C. MCCOY, JR., of counsel) all of Cleveland, Ohio, for appellant.

CLARENCE W. MOORE (J. SCHIMMEL of counsel) for Commissioner of Patents.

Before JOHNSON, Chief Judge, and WORLEY, RICH, and JACKSON (retired), Associate Judges.

RICH, Judge.

This is an appeal from the decision of the Patent Office Board of Appeals in which it affirmed the primary examiner's rejection of claims 1-4, 12, 14 and 15, and reversed the examiner as to claim 18, which claim was allowed.

Claims 1 and 18 are representative:

1. An isopropenyl benzene having only two substituents both of which are attached directly to the nuclear carbon atoms and neither of which are attached to carbon atoms next adjacent that carrying the isopropenyl group; said substituents being further characterized in that they are both ortho-para directing groups which do not appreciably activate the benzene ring, said isopropenyl benzene being further characterized in that it is free from more than 20 per cent of unpolymerizable impurities.

18. 3,4-dichloro-isopropenyl benzene said isopropenyl benzene being further characterized in that it is free from more than 20 per cent of unpolymerizable impurities.

We need not discuss the invention beyond pointing out that the application contains broad or generic claims to certain isopropenyl benzenes, such as claim 1, and also specific claims, such as claim 18 to species within the scope of the broad claims. Claims 1-4 and 14 are the broad claims. Claims 12 and 15 are under rejection as to non-elected species and are not before us.

The parties to this appeal are in agreement that there is no dispute as to the facts, which present for our consideration a single question of law. This question, as we shall show, is one on which there is today, as the Solicitor for the Patent Office stated at the hearing, a difference of opinion in the Board of Appeals which our decision in this case should resolve. These are the pertinent facts:

1. Only one reference is relied on, the United States patent to Amos et al., No. 2,486,379, issued November 1, 1949 on an application filed July 22, 1946.

2. The Amos et al. patent discloses but does not claim the compound "alpha-methyl-3, 4-dichlorostyrene" which is the same thing as 3, 4-dichloro-isopropenyl benzene, the compound of

allowed claim 18. Amos et al. discloses nothing else pertinent to the claimed invention.

3. The applicant submitted several affidavits under Patent Office Rule 131 (formerly Rule 75) which satisfied the Board that he had made the compound as described in claim 18, but only that compound, prior to the filing date of the Amos et al. patent, for which reason it held that claim to be allowable, reversing the examiner on this point.

4. The Board nevertheless sustained the rejection of the broad claims *on the Amos et al. patent,* notwithstanding the antedating under Rule 131 of everything it discloses pertinent to the claimed subject matter.

[1] The question before us is whether, under these circumstances, the rejection of the broad claims on Amos et al. is proper. Restated, the question is: When a domestic patent discloses only a single species of an invention and the applicant submits an affidavit under Rule 131 showing completion of the invention of that species prior to the effective date of the reference (which does not claim it), can that reference be used as the basis of the rejection of generic claims in the application?

Appellant has cited Ex parte Burt, 89 USPQ 186 (Bd. App., 1950), as controlling. In that case the applicant filed an affidavit under Rule 75 (now Rule 131), in support of generic claims, showing completion of the invention of the same species of invention as that disclosed in certain references before the effective date of the earliest reference. In reversing the examiner's holding that the affidavit failed to overcome the references as to the generic claims, the Board said, 89 USPQ at 188:

> We are of the opinion that the examiner is in error in holding the affidavit insufficient to overcome these references, because it is not ordinarily the function of an affidavit under old Rule 75 to show the invention *as claimed* has been reduced to practice prior to the date of the reference which it aims to overcome. *It is sufficient if it shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the appellant prior to the date of the reference.* [Emphasis added.]

It is noted that old Rule 75, as does present Rule 131, required a showing of "completion *of the invention* in this country" before the effective date of the reference. (Emphasis ours.)

In the present case a different panel of the Board has held,

> It is now well settled that a showing under Rule 131 establishing priority as to a common species is not necessarily sufficient to obtain allowance of a generic claim.

And further, on reconsideration, the Board said,

> To obtain allowance of generic claims here appellant must establish that he was in possession of the *generic* invention prior to the effective date of the reference, i.e. the affidavits under Rule 131 must show as much as the minimum required by a patent specification to furnish such support.

It is evident that these statements, particularly the latter, are not in harmony with what was said in Ex parte Burt, if not directly contrary thereto.

To support its view of the law in this case the Board relied on the following cases: In re Steenbock, 23 C.C.P.A. (Patents) 1244, 30 USPQ 45, 83 F.2d 912; Ex parte Fryling, 75 USPQ 9, 1947 C.D. 5 (Bd. App. 1947); Ex parte Pritchard et al., 103 USPQ 160 (Bd. App. 1952); Ex parte Young et al., 104 USPQ 181 (Bd. App. 1954). The first case was a decision of this court. The others were all decisions of the Board, the opinions in which all rely, to a greater or less extent, on In re Steenbock as a controlling authority. It is also observed that in Ex parte Young the Board indicated a belief that Ex parte Burt, relied on in that case by the appellant, contained language which might be interpreted "as contrary to the terms of Rule 131," having reference no doubt to the passage from Ex parte Burt quoted above. Insofar as this was so, the Board said, "it must be deemed without authority since this Board does not have any authority to modify or ignore the requirements of the rules established pursuant to the statutes." We shall advert to this point later.

In none of the above Board decisions was the fact situation the same as that in this case.

In Ex parte Fryling the affidavits under Rule 131 showed, first, a prior reduction to practice of one species disclosed by the reference and, second, a conception, prior to the effective date of the reference, of a second species, coupled by diligence with a later reduction to practice, which established priority as to the second species also. The Board *allowed* the generic claims, finding that the affidavits showed completion of a generic invention prior to the effective date of the reference.

In Ex parte Pritchard the applicant attempted to swear back of a reference by showing reduction to practice of "a

particular species." He was allowed a claim to that species. But on the appeal he was asking for broader claims, the subject matter of which the Board held to be *substantially shown in the reference.* Thus all pertinent subject matter in the reference had not been antedated and it was still a good reference against the broad claims.

In Ex parte Young an affidavit was accepted as establishing prior invention of a "particular species" but was held not to establish *priority* as to claimed generic subject matter. It is impossible to tell from the opinion how much pertinent disclosure the reference contained other than that which was covered by the showing of the affidavit, but it is obvious that it was considerable. That being so, *there was still anticipatory matter in the reference, not antedated,* by reason of which it could remain a good reference.

The decisions reached on the facts presented in these three Board decisions relied on in this case are, therefore, not, on the basis of their facts, precedents for the decision of the Board in this case.

Of the cases relied on by the Board we have left for consideration the decision of this court in In re Steenbock, supra. Notwithstanding its repeated citation by the Board in cases involving swearing-back affidavits, as a controlling authority for what they must contain to support generic claims, we are unable to see that the opinion either says anything about or makes any holding on this point. To be sure, it refers to the facts that some specific claims had been allowed as a result of a Rule 75 affidavit, but that affidavit had nothing whatever to do with the broad claims on appeal. All of those claims were rejected because there was no supporting disclosure in any of the copending earlier applications on which the appellant was attempting to rely and consequently each of three references constituted a statutory bar, having been published more than two years prior to the filing date of the involved application.

The much quoted statement from this court's opinion in In re Steenbock was nothing more than a reiteration of the then well-established rule that, in composition of matter cases, "the disclosure of a species in a cited reference is sufficient to prevent a later applicant from obtaining generic claims, although the disclosure in an application of a species may not be sufficient basis for a generic claim," (which seems to be an unnecessary confusion of two distinct propositions of law). The metamorphosis of this statement, through repeated application to unrelated problems without due regard to the circumstances of its origin, into the proposition here applied by the Board that a Rule 131 (or 75) affidavit, to support generic claims, "must show as much as the minimum required by [of] a patent specification to furnish such support," without any regard for what the reference sworn back of discloses, is wholly unwarranted.

As far as the cases relied on by the Board are concerned, we hold that they do not support its affirmance of the rejection of applicant's broad claims on the Amos et al. reference, all pertinent disclosure in that reference having been antedated.

An earlier Board decision than those considered above which is in accord with our view is Ex parte Clark, 60 USPQ 72, 73, (Bd. App. 1943), cited by neither party, wherein, as here, an examiner held a Rule 75 affidavit inadequate to overcome rejection of a generic (Markush) claim on a reference disclosing only one species which the affidavit had antedated, citing In re Steenbock, supra. In reversing, the Board said, "it was only necessary for applicant to overcome the *disclosure* of that patent to *eliminate* it as a reference." (Emphasis ours.) It correctly distinguished In re Steenbock on the ground that the refusal of generic claims in that case was "For lack of disclosure in the specification rather than lack of showing in the affidavit under Rule 75." To the same effect is Ex parte Clifford, 34 USPQ 232, (Bd. App. 1936, prior to In re Steenbock); see especially the concurring opinion of Thurber, Examiner in Chief, whose dissenting opinion in Ex parte Sebrell, 36 USPQ 80 (Bd. App. 1937), may have contributed to the schism which has developed in the Board. In this dissent he pointed out that when a reference has a generic disclosure, then the affidavit to overcome it should show prior completion of the generic invention to support a generic claim.

There appears to be another basis for the Board's conclusion beside the "prevailing authority," which we have just found to be non-existent, and that is the wording of Rule 131 itself. This point is not clearly brought out in the Board's opinions in this case, but that it is lurking there is evident from what the Board has said on previous occasions in the cases cited by it and in the Board's statement that "the showing must show a reduction to practice of the *claimed* invention." (Emphasis in original.) It is also implicit in the statement, "It is our conclusion from the record presented that appellant was not

in possession of the generic invention at a time prior to the effective date of Amos et al." Wherefore we deem it prudent to express our views on this point, especially since it was argued by the Patent Office Solicitor.

Rule 131, insofar as applicable here, reads:

> When any claim of an application is rejected on reference to a domestic patent which substantially shows or describes but does not claim the rejected invention, * * * and the applicant shall make oath to facts showing a completion *of the invention* in this country before the filing date of the application on which the domestic patent issued, * * * then the patent * * * cited shall not bar the grant of a patent to the applicant, *unless* the date of such patent * * * be more than one year prior to the date on which the application was filed in this country. (Emphasis ours.)

[2] What the Board is here saying, in effect, is that the invention, the completion of which must be shown by a Rule 131 affidavit, is the invention *defined in the claim the applicant is asking for* and, if it is a generic claim, prior completion of the generic invention must be shown, whether or not the reference discloses the generic invention.

We think this is a too literal construction of the rule and not in accord with past practice. See Ex parte Burt and Ex parte Clifford, supra. We are convinced that under the law all the applicant can be required to show is priority with respect to so much of the claimed invention as the references happens to show. When he has done that he has disposed of the reference.

[3] The patent statutes give to inventors the right to a patent upon compliance with their provisions, and neither the rules promulgated by the Patent Office nor the interpretation placed upon them can detract from these rights. 35 U.S.C. 6. Under 35 U.S.C. 102 an ap- [4] plicant is "entitled to a patent unless" it is shown that one or another of the prohibitory provisions therein, or elsewhere in the statute, applies. In the case of a reference, it is [5] fundamental that it is valid only for what it discloses and if the applicant establishes priority with respect to that disclosure, and there is no statutory bar, it is of no effect at all.

[6] What is a "reference"? It is nothing more than a patent or publication cited to show that all or part of the invention for which a patent is sought was in the prior art, either more than a year before the filing date to which the applicant is entitled, in which case it is a "statutory bar" and cannot be sworn back of, or before the ap- [7] plicant's date of invention. When a reference is not a statutory bar, Rule 131 provides a procedure by which the applicant is permitted to show, if he can, that his date of invention was earlier than the date of the reference. The rule must be construed in accordance with the rights given to inventors by statute and this excludes a construction permitting the further use of a reference as a ground of rejection after all pertinent subject matter in it has been antedated to the satisfaction of the Patent Office.

For the foregoing reasons the decision of the Board of Appeals *is reversed.*

JACKSON, Judge, retired was recalled to participate in place of COLE, Judge, absent because of illness.

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44 C.C.P.A. (Patents) 789

Court of Customs and Patent Appeals

In re PENNINGTON

Appl. No. 6250 Decided Feb. 21, 1957

PATENTS

1. Patentability — Anticipation — Combining references (§ 51.205)

Where two or more prior art references are combined to negative patentability, test applied is whether prior art suggests doing what applicant did; it must be considered whether one skilled in art, with references before him, could have made combination of elements claimed without exercise of invention.

2. Patentability—Evidence of—In general (§ 51.451)

In many cases, invention may consist in one or both of (1) conception of general result wished for, and (2) actual means of achieving that result; hence, that applicant's modifications over prior art might not produce what would normally be termed to be new and unexpected results is not determinant inasmuch as essential portion of applicant's contribution was appreciation that maximum efficiency of prior art devices could not be obtained due to specific cause; once having appreciated this problem, it might be that one skilled in art would construct applicant's apparatus without further use of inventive faculty, but

FIGURE 1A[-1]

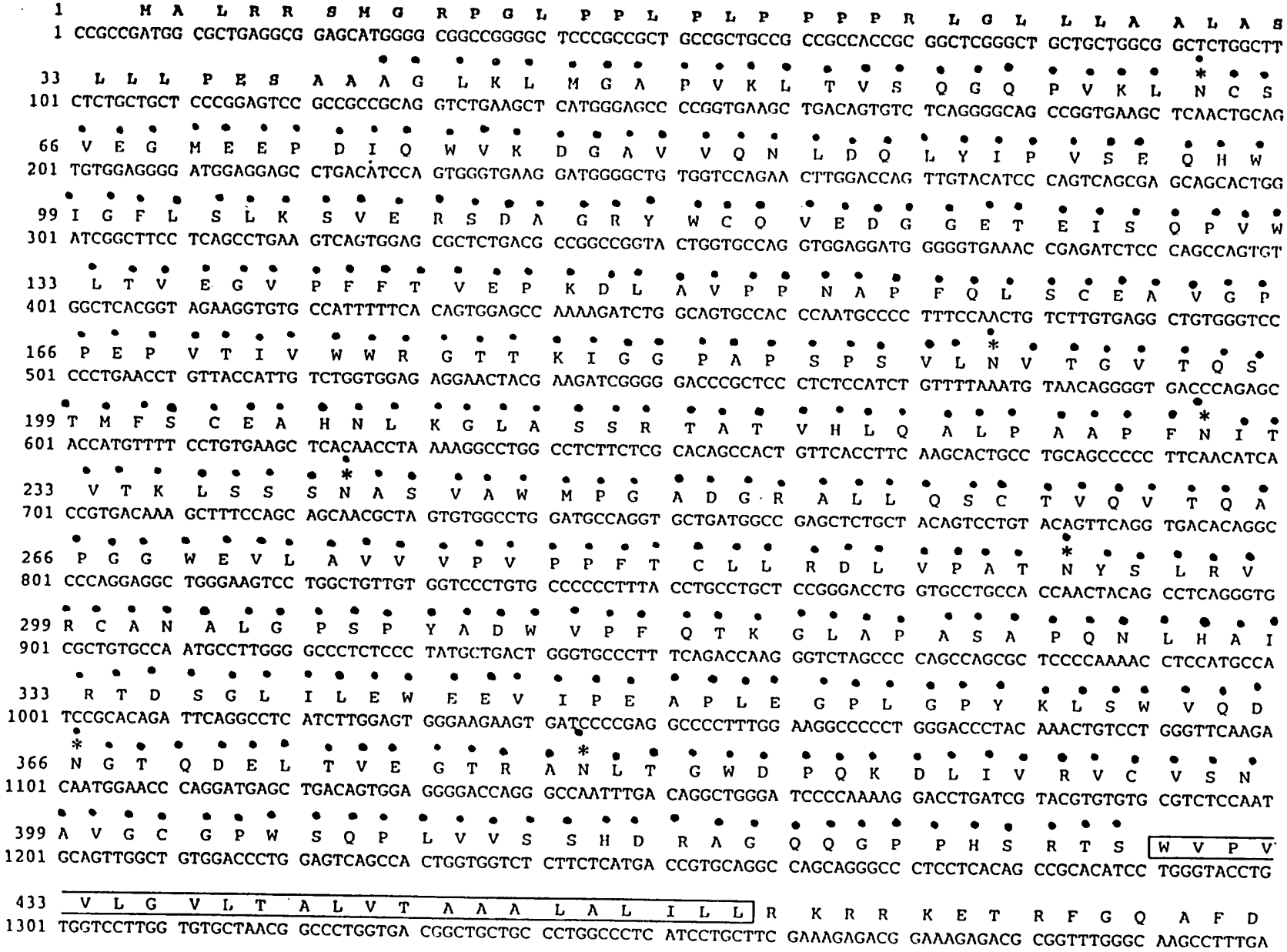
1 M A L R R S M G R P G L P P L P L P P P P R L G L L L A A L A S
1 CCGCCGATGG CGCTGAGGCG GAGCATGGGG CGGCCGGGGC TCCCGCCGCT GCCGCTGCCG CCGCCACCGC GGCTCGGGCT GCTGCTGGCG GCTCTGGCTT
33 L L L P E S A A A G L K L M G A P V K L T V S Q G Q P V K L N C S
101 CTCTGCTGCT CCCGGAGTCC GCCGCCGCAG GTCTGAAGCT CATGGGAGCC CCGGTGAAGC TGACAGTGTC TCAGGGGCAG CCGGTGAAGC TCAACTGCAG
66 V E G M E E P D I Q W V K D G A V V Q N L D Q L Y I P V S E Q H W
201 TGTGGAGGGG ATGGAGGAGC CTGACATCCA GTGGGTGAAG GATGGGGCTG TGGTCCAGAA CTTGGACCAG TTGTACATCC CAGTCAGCGA GCAGCACTGG
99 I G F L S L K S V E R S D A G R Y W C Q V E D G G E T E I S Q P V W
301 ATCGGCTTCC TCAGCCTGAA GTCAGTGGAG CGCTCTGACG CCGGCCGGTA CTGGTGCCAG GTGGAGGATG GGGGTGAAAC CGAGATCTCC CAGCCAGTGT
133 L T V E G V P F F T V E P K D L A V P P N A P F Q L S C E A V G P
401 GGCTCACGGT AGAAGGTGTG CCATTTTTCA CAGTGGAGCC AAAAGATCTG GCAGTGCCAC CCAATGCCCC TTTCCAACTG TCTTGTGAGG CTGTGGGTCC
166 P E P V T I V W W R G T T K I G G P A P S P S V L N V T G V T Q S
501 CCCTGAACCT GTTACCATTG TCTGGTGGAG AGGAACTACG AAGATCGGGG GACCCGCTCC CTCTCCATCT GTTTTAAATG TAACAGGGGT GACCCAGAGC
199 T M F S C E A H N L K G L A S S R T A T V H L Q A L P A A P F N I T
601 ACCATGTTTT CCTGTGAAGC TCACAACCTA AAAGGCCTGG CCTCTTCTCG CACAGCCACT GTTCACCTTC AAGCACTGCC TGCAGCCCCC TTCAACATCA
233 V T K L S S S N A S V A W M P G A D G R A L L Q S C T V Q V T Q A
701 CCGTGACAAA GCTTTCCAGC AGCAACGCTA GTGTGGCCTG GATGCCAGGT GCTGATGGCC GAGCTCTGCT ACAGTCCTGT ACAGTTCAGG TGACACAGGC
266 P G G W E V L A V V V P V P P F T C L L R D L V P A T N Y S L R V
801 CCCAGGAGGC TGGGAAGTCC TGGCTGTTGT GGTCCCTGTG CCCCCCTTTA CCTGCCTGCT CCGGGACCTG GTGCCTGCCA CCAACTACAG CCTCAGGGTG
299 R C A N A L G P S P Y A D W V P F Q T K G L A P A S A P Q N L H A I
901 CGCTGTGCCA ATGCCTTGGG GCCCTCTCCC TATGCTGACT GGGTGCCCTT TCAGACCAAG GGTCTAGCCC CAGCCAGCGC TCCCCAAAAC CTCCATGCCA
333 R T D S G L I L E W E E V I P E A P L E G P L G P Y K L S W V Q D
1001 TCCGCACAGA TTCAGGCCTC ATCTTGGAGT GGGAAGAAGT GATCCCCGAG GCCCCTTTGG AAGGCCCCCT GGGACCCTAC AAACTGTCCT GGGTTCAAGA
366 N G T Q D E L T V E G T R A N L T G W D P Q K D L I V R V C V S N
1101 CAATGGAACC CAGGATGAGC TGACAGTGGA GGGGACCAGG GCCAATTTGA CAGGCTGGGA TCCCCAAAAG GACCTGATCG TACGTGTGTG CGTCTCCAAT
399 A V G C G P W S Q P L V V S S H D R A G Q Q G P P H S R T S W V P V
1201 GCAGTTGGCT GTGGACCCTG GAGTCAGCCA CTGGTGGTCT CTTCTCATGA CCGTGCAGGC CAGCAGGGCC CTCCTCACAG CCGCACATCC TGGGTACCTG
433 V L G V L T A L V T A A A L A L I L L R K R R K E T R F G Q A F D
1301 TGGTCCTTGG TGTGCTAACG GCCCTGGTGA CGGCTGCTGC CCTGGCCCTC ATCCTGCTTC GAAAGAGACG GAAAGAGACG CGGTTTGGGC AAGCCTTTGA

FIGURE [1A-2] 1B

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 466 S V M A R G E P A V H F R A A R S F N R E R P E R I E A T L D S L
1401 CAGTGTCATG GCCCGGGGAG AGCCAGCCGT TCACTTCCGG GCAGCCCGGT CCTTCAATCG AGAAAGGCCC GAGCGCATCG AGGCCACATT GGACAGCTTG

 499 G I S D E L K E K L E D V L I P E Q Q F T L G R M L G K G E F G S V
1501 GGCATCAGCG ATGAACTAAA GGAAAAACTG GAGGATGTGC TCATCCCAGA GCAGCAGTTC ACCCTGGGCC GGATGTTGGG CAAAGGAGAG TTTGGTTCAG

 533 R E A Q L K Q E D G S F V K V A V K M L K A D I I A S S D I E E F
1601 TGCGGGAGGC CCAGCTGAAG CAAGAGGATG GCTCCTTTGT GAAAGTGGCT GTGAAGATGC TGAAAGCTGA CATCATTGCC TCAAGCGACA TTGAAGAGTT

 566 L R E A A C M K E F D H P H V A K L V G V S L R S R A K G R L P I
1701 CCTCAGGGAA GCAGCTTGCA TGAAGGAGTT TGACCATCCA CACGTGGCCA AACTTGTTGG GGTAAGCCTC CGGAGCAGGG CTAAAGGCCG TCTCCCCATC

 599 P M V I L P F M K H G D L H A F L L A S R I G E N P F N L P L Q T L
1801 CCCATGGTCA TCTTGCCCTT CATGAAGCAT GGGGACCTGC ATGCCTTCCT GCTCGCCTCC CGGATTGGGG AGAACCCCTT TAACCTACCC CTCCAGACCC

 633 I R F M V D I A C G M E Y L S S R N F I H R D L A A R N C M L A E
1901 TGATCCGGTT CATGGTGGAC ATTGCCTGCG GCATGGAGTA CCTGAGCTCT CGGAACTTCA TCCACCGAGA CCTGGCTGCT CGGAATTGCA TGCTGGCAGA

 666 D M T V C V A D F G L S R K I Y S G D Y Y R Q G C A S K L P V K W
2001 GGACATGACA GTGTGTGTGG CTGACTTCGG ACTCTCCCGG AAGATCTACA GTGGGGACTA CTATCGTCAA GGCTGTGCCT CCAAACTGCC TGTCAAGTGG

 699 L A L E S L A D N L Y T V Q S D V W A F G V T M W E I M T R G Q T P
2101 CTGGCCCTGG AGAGCCTGGC CGACAACCTG TATACTGTGC AGAGTGACGT GTGGGCGTTC GGGGTGACCA TGTGGGAGAT CATGACACGT GGGCAGACGC

 733 Y A G I E N A E I Y N Y L I G G N R L K Q P P E C M E D V Y D L M
2201 CATATGCTGG CATCGAAAAC GCTGAGATTT ACAACTACCT CATTGGCGGG AACCGCCTGA AACAGCCTCC GGAGTGTATG GAGGACGTGT ATGATCTCAT

 766 Y Q C W S A D P K Q R P S F T C L R M E L E N I L G Q L S V L S A
2301 GTACCAGTGC TGGAGTGCTG ACCCCAAGCA GCGCCCGAGC TTTACTTGTC TGCGAATGGA ACTGGAGAAC ATCTTGGGCC AGCTGTCTGT GCTATCTGCC

 799 S Q D P L Y I N I E R A E E P T A G G S L E L P G R D Q P Y S G A G
2401 AGCCAGGACC CCTTATACAT CAACATCGAG AGAGCTGAGG AGCCCACTGC GGGAGGCAGC CTGGAGCTAC CTGGCAGGGA TCAGCCCTAC AGTGGGGCTG

 833 D G S G M G A V G G T P S D C R Y I L T P G G L A E Q P G Q A E H
2501 GGGATGGCAG TGGCATGGGG GCAGTGGGTG GCACTCCCAG TGACTGTCGG TACATACTCA CCCCCGGAGG GCTGGCTGAG CAGCCAGGGC AGGCAGAGCA

 866 Q P E S P L N E T Q R L L L L Q Q G L L P H S S C O
2601 CCAGCCAGAG AGTCCCCTCA ATGAGACACA GAGGCTTTTG CTGCTGCAGC AAGGGCTACT GCCACACAGT AGCTGTTAGC CCACAGGCAG AGGGCATCGG

2701 GGCCATTTGG CCGGCTCTGG TGGCCACTGA GCTGGCTGAC TAAGCCCCGT CTGACCCCAG CCCAGACAGC AAGGTGTGGA GGCTCCTGTG GTAGTCCTCC

2801 CAAGCTGTGC TGGGAAGCCC GGACTGACCA AATCACCCAA TCCCAGTTCT TCCTGCAACC ACTCTGTGGC CAGCCTGGCA TCAGTTTAGG CCTTGGCTTG
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FIGURE [1A-3] 1C

2901 ATGGAAGTGG GCCAGTCCTG GTTGTCTGAA CCCAGGCAGC TGGCAGGAGT GGGGTGGTTA TGTTTCCATG GTTACCATGG GTGTGGATGG CAGTGTGGGG

3001 AGGGCAGGTC CAGCTCTGTG GGCCCTACCC TCCTGCTGAG CTGCCCCTGC TGCTTAAGTG CATGCATTGA GCTGCCTCCA GCCTGGTGGC CCAGCTATTA

3101 CCACACTTGG GGTTTAAATA TCCAGGTGTG CCCCTCCAAG TCACAAAGAG ATGTCCTTGT AATATTCCCT TTTAGGTGAG GGTTGGTAAG GGGTTGGTAT

3201 CTCAGGTCTG AATCTTCACC ATCTTTCTGA TTCCGCACCC TGCCTACGCC AGGAGAAGTT GAGGGGAGCA TGCTTCCCTG CAGCTGACCG GGTCACACAA

3301 AGGCATGCTG GAGTACCCAG CCTATCAGGT GCCCCTCTTC CAAAGGCAGC GTGCCGAGCC AGCAAGAGGA AGGGGTGCTG TGAGGCTTGC CCAGGAGCAA

3401 GTGAGGCCGG AGAGGAGTTC AGGAACCCTT CTCCATACCC ACAATCTGAG CACGCTACCA AATCTCAAAA TATCCTAAGA CTAACAAAGG CAGCTGTGTC

3501 TGAGCCCAAC CCTTCTAAAC GGTGACCTTT AGTGCCAACT TCCCCTCTAA CTGGACAGCC TCTTCTGTCC CAAGTCTCCA GAGAGAAATC AGGCCTGATG

3601 AGGGGGAATT C

FIGURE [1B-1] 2A

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1                                                                                    M A L      R R S M     G W P     G L R
1    CCTCCGCCAC CCTCCTCTCA GCGCTCGCGG GCCGGGCCCG GCATGGTGCG CGTCGCCGCC GATGGCGCTG AGGCGGAGCA TGGGGTGGCC GGGGCTCCGG

14   P L L L   A G L   A S L   L L P G   S A A   A G L   K L M G   A P V   K M T   V S Q G
101  CCGCTGCTGC TGGCGGGACT GGCTTCTCTG CTGCTCCCCG GGTCTGCGGC CGCAGGCCTG AAGCTCATGG GCGCCCCAGT GAAGATGACC GTGTCTCAGG

48   Q P V   K L N   C S V E   G M E   D P D   I H W M   K D G   T V V   Q N A S   Q V S
201  GGCAGCCAGT GAAGCTCAAC TGCAGCGTGG AGGGGATGGA GGACCCTGAC ATCCACTGGA TGAAGGATGG CACCGTGGTC CAGAATGCAA GCCAGGTGTC

81   I S I   S E H S   W I G   L L S   L K S V   E R S   D A G   L Y W C   Q V K   D G E
301  CATCTCCATC AGCGAGCACA GCTGGATTGG CTTACTCAGC CTAAAGTCAG TGGAGCGGTC TGATGCTGGC CTGTACTGGT GCCAGGTGAA GGATGGGGAG

114  E T K I   S Q S   V W L   T V E G   V P F   F T V   E P K D   L A V   P P N   A P F Q
401  GAAACCAAGA TCTCTCAGTC AGTATGGCTC ACTGTCGAAG GTGTGCCATT CTTCACAGTG GAACCAAAAG ATCTGGCGGT GCCACCCAAT GCCCCTTTTC

148  L S C   E A V   G P P E   P V T   I Y W   W R G L   T K V   G G P   A P S P   S V L
501  AGCTGTCTTG TGAGGCTGTG GGTCCTCCAG AACCCGTAAC CATTTACTGG TGGAGAGGAC TCACTAAGGT TGGGGGACCT GCTCCCTCTC CCTCTGTTTT

181  N V T   G V T Q   R T E   F S C   E A R N   I K G   L A T   S R P A   I V R   L Q A
601  AAATGTGACA GGAGTGACCC AGCGCACAGA GTTTTCTTGT GAAGCCCGCA ACATAAAAGG CCTGGCCACT TCCCGACCAG CCATTGTTCG CCTTCAAGCA

214  P P A A   P F N   T T V   T T I S   S Y N   A S V   A W V P   G A D   G L A   L L H S
701  CCGCCTGCAG CTCCTTTCAA CACCACAGTA ACAACGATCT CCAGCTACAA CGCTAGCGTG GCCTGGGTGC CAGGTGCTGA CGGCCTAGCT CTGCTGCATT

248  C T V   Q V A   H A P G   E W E   A L A   V V V P   V P P   F T C   L L R N   L A P
801  CCTGTACTGT ACAGGTGGCA CACGCCCCAG GAGAATGGGA GGCCCTTGCT GTTGTGGTTC CTGTGCCACC TTTTACCTGC CTGCTTCGGA ACTTGGCCCC

281  A T N   Y S L R   V R C   A N A   L G P S   P Y G   D W V   P F Q T   K G L   A P A
901  TGCCACCAAC TACAGCCTTA GGGTGCGCTG TGCCAATGCC TTGGGCCCTT CTCCCTACGG CGACTGGGTG CCCTTTCAGA CAAAGGGCCT AGCGCCAGCC

314  R A P Q   N F H   A I R   T D S G   L I L   E W E   E V I P   E D P   G E G   P L G P
1001 AGAGCTCCTC AGAATTTCCA TGCCATTCGT ACCGACTCAG GCCTTATCCT GGAATGGGAA GAAGTGATTC CTGAAGACCC TGGGGAAGGC CCCCTAGGAC

348  Y K L   S W V   Q E N G   T Q D   E L M   V E G T   R A N   L T D   W D P Q   K D L
1101 CTTATAAGCT GTCCTGGGTC CAAGAAAATG GAACCCAGGA TGAGCTGATG GTGGAAGGGA CCAGGGCCAA TCTGACCGAC TGGGATCCCC AGAAGGACCT

381  I L R   V C A S   N A I   G D G   P W S Q   P L V   V S S   H D H A   G R Q   G P P
1201 GATTTTGCGT GTGTGTGCCT CCAATGCAAT TGGTGATGGG CCCTGGAGTC AGCCACTGGT GGTGTCTTCT CATGACCATG CAGGGAGGCA GGGCCCTCCC

414  H S R T   S [W V   P V V   L G V L   T A L   I T A   A A L A   L I L   L] R K   R R K E
1301 CACAGCCGCA CATCCTGGGT GCCTGTGGTC CTGGGCGTGC TCACCGCCCT GATCACAGCT GCTGCCTTGG CCCTCATCCT GCTTCGGAAG AGACGCAAGG

448  T R F   G Q A   F D S V   M A R   G E P   A V H F   R A A   R S F   N R E R   P E R
1401 AGACGCGTTT CGGGCAAGCC TTTGACAGTG TCATGGCCCG AGGGGAGCCA GCTGTACACT TCCGGGCAGC CCGATCTTTC AATCGAGAAA GGCCTGAACG
```

FIGURE [1B-2] 2B

```
481   I  E  A  T  L  D  S  L  G  I  S  D  E  L  K  E  K  L  E  D  V  L  I  P  E  Q  Q  F  T  L  G  R  M
1501  CATTGAGGCC ACATTGGATA GCCTGGGCAT CAGCGATGAA TTGAAGGAAA AGCTGGAGGA TGTCCTCATT CCAGAGCAGC AGTTCACCCT CGGTCGGATG

514   L  G  K  G  E  F  G  S  V  R  E  A  Q  L  K  Q  E  D  G  S  F  V  K  V  A  V  K  M  L  K  A  D  I  I
1601  TTGGGCAAAG GAGAGTTTGG ATCAGTGCGG GAAGCCCAGC TAAAGCAGGA AGATGGCTCC TTCGTGAAAG TGGCAGTGAA GATGCTGAAA GCTGACATCA

548   A  S  S  D  I  E  E  F  L  R  E  A  A  C  M  K  E  F  D  H  P  H  V  A  K  L  V  G  V  S  L  R  S
1701  TTGCCTCAAG CGACATAGAA GTGTTCCTCC GGGAAGCAGC TTGCATGAAG GAGTTTGACC ATCCACACGT GGCCAAGCTT GTTGGGGTGA GCCTCCGGAG

581   R  A  K  G  R  L  P  I  P  M  V  I  L  P  F  M  K  H  G  D  L  H  A  F  L  L  A  S  R  I  G  E  N
1801  CAGGGCTAAA GGTCGTCTCC CCATTCCCAT GGTCATCCTG CCCTTCATGA AACATGGAGA CTTGCACGCC TTTCTGCTCG CCTCCCGAAT CGGGGAGAAC

614   P  F  N  L  P  L  Q  T  L  V  R  F  M  V  D  I  A  C  G  M  E  Y  L  S  S  R  N  F  I  H  R  D  L  A
1901  CCTTTTAACC TGCCCCTGCA GACCCTGGTC CGGTTCATGG TGGACATTGC CTGTGGCATG GAGTACCTGA GCTCCCGGAA CTTCATCCAC CGAGACCTAG

648   A  R  N  C  M  L  A  E  D  M  T  V  C  V  A  D  F  G  L  S  R  K  I  Y  S  G  D  Y  Y  R  Q  G  C
2001  CAGCTCGGAA TTGCATGCTG GCCGAGGACA TGACAGTGTG TGTGGCTGAT TTTGGACTCT CTCGGAAAAT CTATAGCGGG GACTATTATC GTCAGGGCTG

681   A  S  K  L  P  V  K  W  L  A  L  E  S  L  A  D  N  L  Y  T  V  H  S  D  V  W  A  F  G  V  T  M  W
2101  TGCCTCCAAA TTGCCCGTCA AGTGGCTGGC CCTGGAGAGC TTGGCTGACA ACTTGTATAC TGTACACAGT GATGTGTGGG CCTTCGGGGT GACCATGTGG

714   E  I  M  T  R  G  Q  T  P  Y  A  G  I  E  N  A  E  I  Y  N  Y  L  I  G  G  N  R  L  K  Q  P  P  E  C
2201  GAGATCATGA CTCGTGGGCA GACGCCATAT GCTGGCATTG AAAATGCTGA GATTTACAAC TACCTCATCG GCGGGAACCG CCTGAAGCAG CCTCCGGAGT

748   M  E  E  V  Y  D  L  M  Y  Q  C  W  S  A  D  P  K  Q  R  P  S  F  T  C  L  R  M  E  L  E  N  I  L
2301  GCATGGAGGA AGTGTATGAT CTCATGTACC AGTGCTGGAG CGCCGACCCC AAGCAGCGCC CAAGCTTCAC GTGTCTGCGA ATGGAACTGG AGAACATTCT

781   G  H  L  S  V  L  S  T  S  Q  D  P  L  Y  I  N  I  E  R  A  E  Q  P  T  E  S  G  S  P  E  L  H  C
2401  GGGCCACCTG TCTGTGCTGT CCACCAGCCA GGACCCCTTG TACATCAACA TTGAGAGAGC TGAGCAGCCT ACTGAGAGTG GCAGCCCTGA GCTGCACTGT

814   G  E  R  S  S  S  E  A  G  D  G  S  G  V  G  A  V  G  G  I  P  S  D  S  R  Y  I  F  S  P  G  G  L  S
2501  GGAGAGCGAT CCAGCAGCGA GGCAGGGGAC GGCAGTGGCG TGGGGGCAGT AGGTGGCATC CCCAGTGACT CTCGGTACAT CTTCAGCCCC GGAGGGCTAT

848   E  S  P  G  Q  L  E  Q  Q  P  E  S  P  L  N  E  N  Q  R  L  L  L  L  Q  Q  G  L  L  P  H  S  S  C
2601  CCGAGTCACC AGGGCAGCTG GAGCAGCAGC CAGAAAGCCC CCTCAATGAG AACCAGAGGC TGTTGTTGCT GCAGCAAGGG CTACTGCCTC ACAGTAGCTG

881   O
2701  TTAACCCTCA GGCAGAGGAA AGTTGGGGCC CCTGGCTCTG CTGACCGCTG CGCTGCCTGA CTAGGCCCAG TCTGATCACA GCCCAGGCAG CAAGGTATGG

2801  AGGCTCCTGT GGTAGCCCTC CCAAGCTGTG TGGCGCCTGG ACGGACCAAA TTGCCCAATC CCAGTTCTTC CTGCAGCCGC TCTGGCCAGC CTGGCATCAG

2901  TTCAGGCCTT GGCTTAGAGG AGGTGAGCCA GAGCTGGTTG CCTGAATGCA GGCAGCTGGC AGGAGGGGAG GGTGGCTATG TTTCCATGGG TACCATGGGT

3001  GTGGATGGCA GTAAGGGAGG GTAGCAACAG CCTGTGGGCC CCTACCCTCC TGGCTGAGCT GCTCCTACTT TAGTGCATGC TTGGAGCCGC CTGCAGCCTG

3101  GAACTCAGCA CTGCCCACCA CACTTGGGCC GAAATGCCAG GTTTGCCCCT CTTAAGTCAC AAAGAGATGT CCATGTATTG TTCCCTTTTA GGTGATGATT
```

FIGURE [1B-3] 2C

3201 AGGAAGGGAT TGGCACACTT GGGTCCCTAA GCCCTATGGC AGGAAATGGT GGGATATTCT CAGGTCTGAA TCCTCATCAT CTTCCTGATT CCCCACCCTG

3301 CAAAGGCCTG GAACTGGCTG TGGGGCTCTG ACGCATGCTG AAGGACAAAA GGTTACAGAG ATCCGACTTC AAAAGGCAGG GTCTGAGTCT GGCAGGTGGA

3401 GAGGTGCTAA GGGGCTGGCC CAGGAGTCAG GCATTTCAGG ACCCCTCCAA GCTTCTACAG TCTGTCTGAG CATGCTACCA AGCCCCCAGA TACCCCAAAA

3501 CTAACAGAGG CAGTTTTGTC TGAGCCCAGC CCTCCCACAT GATGACCCTT AGGTCTACCC TCCTCTCTAA ATGGACATCC TCGTTTGTCC CAAGTCTCCA

3601 GAGAGACTAC TGATGGCTGA TGTGGGTAAG AAAAGTTCCA GGAACCAGGG CTGGGGTGGA ACCAGGGCTG GGGTCGAGGC AGGCTCTTGG GCAGGCTCTT

3701 GCTGTTAGGA ACATTTCTAA GCTATTAAGT TGCTGTTTCA AAACAAATAA AATTGAAACA TAAAGAATCA AAAAAAAAAA AAAAA

FIGURE [2-1] 3A

```
   1 GAATTCTCGA GTCGACGTTG GACTTGAAGG AATGCCAAGA GATGCTGCCC

  51 CCACCCCCTT AGGCCCGAGG GATCAGGAGC TATGGGACCA GAGGCCCTGT
   1                                    MetGlyPro GluAlaLeuSer
                                                       ******

 101 CATCTTTACT GCTGCTGCTC TTGGTGGCAA GTGGAGATGC TGACATGAAG
   8   SerLeuLe uLeuLeuLeu LeuValAlaS erGlyAspAl aAspMetLys
       ******** ********** ********** *****

 151 GGACATTTTG ATCCTGCCAA GTGCCGCTAT GCCCTGGGCA TGCAGGACCG
  24 GlyHisPheA spProAlaLy sCysArgTyr AlaLeuGlyM etGlnAspArg

 201 GACCATCCCA GACAGTGACA TCTCTGCTTC CAGCTCCTGG TCAGATTCCA
  41  ThrIlePro AspSerAspI leSerAlaSe rSerSerTrp SerAspSerThr

 251 CTGCCGCCCG CCACAGCAGG TTGGAGAGCA GTGACGGGGA TGGGGCCTGG
  58   AlaAlaAr gHisSerArg LeuGluSerS erAspGlyAs pGlyAlaTrp

 301 TGCCCCGCAG GGTCGGTGTT TCCCAAGGAG GAGGAGTACT TGCAGGTGGA
  74 CysProAlaG lySerValPh eProLysGlu GluGluTyrL euGlnValAsp

 351 TCTACAACGA CTGCACCTGG TGGCTCTGGT GGGCACCCAG GGACGGCATG
  91  LeuGlnArg LeuHisLeuV alAlaLeuVa lGlyThrGln GlyArgHisAla

 401 CCGGGGGCCT GGGCAAGGAG TTCTCCCGGA GCTACCGGCT GCGTTACTCC
 108   GlyGlyLe uGlyLysGlu PheSerArgS erTyrArgLe uArgTyrSer

 451 CGGGATGGTC GCCGCTGGAT GGGCTGGAAG GACCGCTGGG GTCAGGAGGT
 124 ArgAspGlyA rgArgTrpMe tGlyTrpLys AspArgTrpG lyGlnGluVal

 501 GATCTCAGGC AATGAGGACC CTGAGGGAGT GGTGCTGAAG GACCTTGGGC
 141  IleSerGly AsnGluAspP roGluGlyVa lValLeuLys AspLeuGlyPro

 551 CCCCCATGGT TGCCCGACTG GTTCGCTTCT ACCCCCGGGC TGACCGGGTC
 158   ProMetVa lAlaArgLeu ValArgPheT yrProArgAl aAspArgVal

 601 ATGAGCGTCT GTCTGCGGGT AGAGCTCTAT GGCTGCCTCT GGAGGGATGG
 174 MetSerValC ysLeuArgVa lGluLeuTyr GlyCysLeuT rpArgAspGly

 651 ACTCCTGTCT TACACCGCCC CTGTGGGGCA GACAATGTAT TTATCTGAGG
 191  LeuLeuSer TyrThrAlaP roValGlyGl nThrMetTyr LeuSerGluAla

 701 CCGTGTACCT CAACGACTCC ACCTATGACG GACATACCGT GGGCGGACTG
 208   ValTyrLe uAsnAspSer ThrTyrAspG lyHisThrVa lGlyGlyLeu

 751 CAGTATGGGG GTCTGGGCCA GCTGGCAGAT GGTGTGGTGG GGCTGGATGA
 224 GlnTyrGlyG lyLeuGlyGl nLeuAlaAsp GlyValValG lyLeuAspAsp

 801 CTTTAGGAAG AGTCAGGAGC TGCGGGTCTG GCCAGGCTAT GACTATGTGG
 241  PheArgLys SerGlnGluL euArgValTr pProGlyTyr AspTyrValGly

 851 GATGGAGCAA CCACAGCTTC TCCAGTGGCT ATGTGGAGAT GGAGTTTGAG
 258   TrpSerAs nHisSerPhe SerSerGlyT yrValGluMe tGluPheGlu
```

FIGURE [2-2] 3B

```
 901 TTTGACCGGC TGAGGGCCTT CCAGGCTATG CAGGTCCACT GTAACAACAT
 274 PheAspArgL euArgAlaPh eGlnAlaMet GlnValHisC ysAsnAsnMet

 951 GCACACGCTG GGAGCCCGTC TGCCTGGCGG GGTGGAATGT CGCTTCCGGC
 291  HisThrLeu GlyAlaArgL euProGlyGl yValGluCys ArgPheArgArg

1001 GTGGCCCTGC CATGGCCTGG GAGGGGGAGC CCATGCGCCA CAACCTAGGG
 308   GlyProAl aMetAlaTrp GluGlyGluP roMetArgHi sAsnLeuGly

1051 GGCAACCTGG GGGACCCCAG AGCCCGGGCT GTCTCAGTGC CCCTTGGCGG
 324 GlyAsnLeuG lyAspProAr gAlaArgAla ValSerValP roLeuGlyGly

1101 CCGTGTGGCT CGCTTTCTGC AGTGCCGCTT CCTCTTTGCG GGGCCCTGGT
 341  ArgValAla ArgPheLeuG lnCysArgPh eLeuPheAla GlyProTrpLeu

1151 TACTCTTCAG CGAAATCTCC TTCATCTCTG ATGTGGTGAA CAATTCCTCT
 358   LeuPheSe rGluIleSer PheIleSerA spValValAs nAsnSerSer

1201 CCGGCACTGG GAGGCACCTT CCCGCCAGCC CCCTGGTGGC CGCCTGGCCC
 374 ProAlaLeuG lyGlyThrPh eProProAla ProTrpTrpP roProGlyPro

1251 ACCTCCCACC AACTTCAGCA GCTTGGAGCT GGAGCCCAGA GGCCAGCAGC
 391  ProProThr AsnPheSerS erLeuGluLe uGluProArg GlyGlnGlnPro

1301 CCGTGGCCAA GCCCGAGGGG AGCCCGACCG CCATCCTCAT CGGCTGCCTG
 408   ValAlaLy sProGluGly SerProThrA laIleLeuIl eGlyCysLeu

1351 GTGGCCATCA TCCTGCTCCT GCTGCTCATC ATTGCCCTCA TGCTCTGGCG
 424 ValAlaIleI leLeuLeuLe uLeuLeuIle IleAlaLeuM etLeuTrpArg

1401 GCTGCACTGG CGCAGGCTCC TCAGCAAGGC TGAACGGAGG GTGTTGGAAG
 441  LeuHisTrp ArgArgLeuL euSerLysAl aGluArgArg ValLeuGluGlu

1451 AGGAGCTGAC GGTTCACCTC TCTGTCCCTG GGGACACTAT CCTCATCAAC
 458   GluLeuTh rValHisLeu SerValProG lyAspThrIl eLeuIleAsn

1501 AACCGCCCAG GTCCTAGAGA GCCACCCCCG TACCAGGAGC CCCGGCCTCG
 474 AsnArgProG lyProArgGl uProProPro TyrGlnGluP roArgProArg

1551 TGGGAATCCG CCCCACTCCG CTCCCTGTGT CCCCAATGGC TCTGCGTTGC
 491  GlyAsnPro ProHisSerA laProCysVa lProAsnGly SerAlaLeuLeu

1601 TGCTCTCCAA TCCAGCCTAC CGCCTCCTTC TGGCCACTTA CGCCCGTCCC
 508   LeuSerAs nProAlaTyr ArgLeuLeuL euAlaThrTy rAlaArgPro

1651 CCTCGAGGCC CGGGCCCCCC CACACCCGCC TGGGCCAAAC CCACCAACAC
 524 ProArgGlyP roGlyProPr oThrProAla TrpAlaLysP roThrAsnThr

1701 CCAGGCCTAC AGTGGGGACT ATATGGAGCC TGAGAAGCCA GGCGCCCCGC
 541  GlnAlaTyr SerGlyAspT yrMetGluPr oGluLysPro GlyAlaProLeu

1751 TTCTGCCCCC ACCTCCCCAG AACAGCGTCC CCCATTATGC CGAGGCTGAC
 558   LeuProPr oProProGln AsnSerValP roHisTyrAl aGluAlaAsp
```

FIGURE [2-3] 3C

```
1801 ATTGTTACCC TGCAGGGCGT CACCGGGGGC AACACCTATG CTGTGCCTGC
 574 IleValThrL euGlnGlyVa lThrGlyGly AsnThrTyrA laValProAla

1851 ACTGCCCCCA GGGGCAGTCG GGGATGGGCC CCCCAGAGTG GATTTCCCTC
 591  LeuProPro GlyAlaValG lyAspGlyPr oProArgVal AspPheProArg

1901 GATCTCGACT CCGCTTCAAG GAGAAGCTTG GCGAGGGCCA GTTTGGGGAG
 608   SerArgLe uArgPheLys GluLysLeuG lyGluGlyGl nPheGlyGlu
           << <                          . .......... .......

1951 GTGCACCTGT GTGAGGTCGA CAGCCCTCAA GATCTGGTCA GTCTTGATTT
 624 ValHisLeuC ysGluValAs pSerProGln AspLeuValS erLeuAspPhe

2001 CCCCCTTAAT GTGCGTAAGG GACACCCTTT GCTGGTAGCT GTCAAGATCT
 641  ProLeuAsn ValArgLysG lyHisProLe uLeuValAla ValLysIleLeu

2051 TACGGCCAGA TGCCACCAAG AATGCCAGGA ATGATTTCCT GAAAGAGGTG
 658   ArgProAs pAlaThrLys AsnAlaArgA snAspPheLe uLysGluVal

2101 AAGATCATGT CGAGGCTCAA GGACCCAAAC ATCATTCGGC TGCTGGGCGT
 674 LysIleMetS erArgLeuLy sAspProAsn IleIleArgL euLeuGlyVal

2151 GTGTGTGCAG GACGACCCCC TCTGCATGAT TACTGACTAC ATGGAGAACG
 691  CysValGln AspAspProL euCysMetIl eThrAspTyr MetGluAsnGly

2201 GCGACCTCAA CCAGTTCCTC AGTGCCCACC AGCTGGAGGA CAAGGCAGCC
 708   AspLeuAs nGlnPheLeu SerAlaHisG lnLeuGluAs pLysAlaAla

2251 GAGGGGGCCC CTGGGGACGG GCAGGCTGCG CAGGGGCCCA CCATCAGCTA
 724 GluGlyAlaP roGlyAspGl yGlnAlaAla GlnGlyProT hrIleSerTyr

2301 CCCAATGCTG CTGCATGTGG CAGCCCAGAT CGCCTCCGGC ATGCGCTATC
 741  ProMetLeu LeuHisValA laAlaGlnIl eAlaSerGly MetArgTyrLeu

2351 TGGCCACACT CAACTTTGTA CATCGGGACC TGGCCACGCG GAACTGCCTA
 758   AlaThrLe uAsnPheVal HisArgAspL euAlaThrAr gAsnCysLeu

2401 GTTGGGGAAA ATTTCACCAT CAAAATCGCA GACTTTGGCA TGAGCCGGAA
 774 ValGlyGluA snPheThrIl eLysIleAla AspPheGlyM etSerArgAsn

2451 CCTCTATGCT GGGGACTATT ACCGTGTGCA GGGCCGGGCA GTGCTGCCCA
 791  LeuTyrAla GlyAspTyrT yrArgValGl nGlyArgAla ValLeuProIle

2501 TCCGCTGGAT GGCCTGGGAG TGCATCCTCA TGGGGAAGTT CACGACTGCG
 808   ArgTrpMe tAlaTrpGlu CysIleLeuM etGlyLysPh eThrThrAla

2551 AGTGACGTGT GGGCCTTTGG TGTGACCCTG TGGGAGGTGC TGATGCTCTG
 824 SerAspValT rpAlaPheGl yValThrLeu TrpGluValL euMetLeuCys

2601 TAGGGCCCAG CCCTTTGGGC AGCTCACCGA CGAGCAGGTC ATCGAGAACG
 841  ArgAlaGln ProPheGlyG lnLeuThrAs pGluGlnVal IleGluAsnAla
```

FIGURE [2-4] 3D

```
2651 CGGGGGAGTT CTTCCGGGAC CAGGGCCGGC AGGTGTACCT GTCCCGGCCG
 858   GlyGluPh ePheArgAsp GlnGlyArgG lnValTyrLe uSerArgPro

2701 CCTGCCTGCC CGCAGGGCCT ATATGAGCTG ATGCTTCGGT GCTGGAGCCG
 874 ProAlaCysP roGlnGlyLe uTyrGluLeu MetLeuArgC ysTrpSerArg

2751 GGAGTCTGAG CAGCGACCAC CCTTTTCCCA GCTGCATCGG TTCCTGGCAG
 891  GluSerGlu GlnArgProP roPheSerGl nLeuHisArg PheLeuAlaGlu
                                                      >>>

2801 AGGATGCACT CAACACGGTG TGAATCACAC ATCCAGCTGC CCCTCCCTCA
 908   AspAlaLe uAsnThrVal

2851 GGGAGTGATC CAGGGGAAGC CAGTGACACT AAAACAAGAG GACACAATGG

2901 CACCTCTGCC CTTCCCCTCC CGACAGCCCA TCACCTCTAA TAGAGGCAGT

2951 GAGACTGCAG AAGCCCCTGT CGCCCACCCA GCTGGTCCTG TGGATGGGAT

3001 CCTCTCCACC CTCCTCTAGC CATCCCTTGG GGAAGGGTGG GGAGAAATAT

3051 AGGATAGACA CTGGACATGG CCCATTGGAG CACCTGGGCC CCACTGGACA

3101 ACACTGATTC CTGGAGAGGT GGCTGCGCCC CCAGCTTCTC TCTCCCTGTC

3151 ACACACTGGA CCCCACTGGC TGAGAATCTG GGGGTGAGGA GGACAAGAAG

3201 GAGAGGAAAA TGTTTCCTTG TGCCTGCTCC TGTACTTGTC CTCAGCTTGG

3251 GCTTCTTCCT CCTCCATCAC CTGAAACACT GGACCTGGGG GTAGCCCCGC

3301 CCCAGCCCTC AGTCACCCCC ACTTCCCACC TGCAGTCTTG TAGCTAGAAC

3351 TTCTCTAAGC CTATACGTTT CTGTGGAGTA AATATTGGGA TTGGGGGGAA

3401 AGAGGGAGCA ACGGCCCATA GCCTTGGGGT TGGACATCTC TAGTGTAGCT

3451 GCCACATTGA TTTTTCTATA ATCACTTGGG GTTTGTACAT TTTTGGGGGG

3501 AGAGACACAG ATTTTTACAC TAATATATGG ACCTAGCTTG AGGCAATTTT

3551 AATCCCCTGC ACTAGGCAGG TAATAATAAA GGTTGAGTTT TCCACAAAAA

3601 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAA
```

FIGURE [3] 4

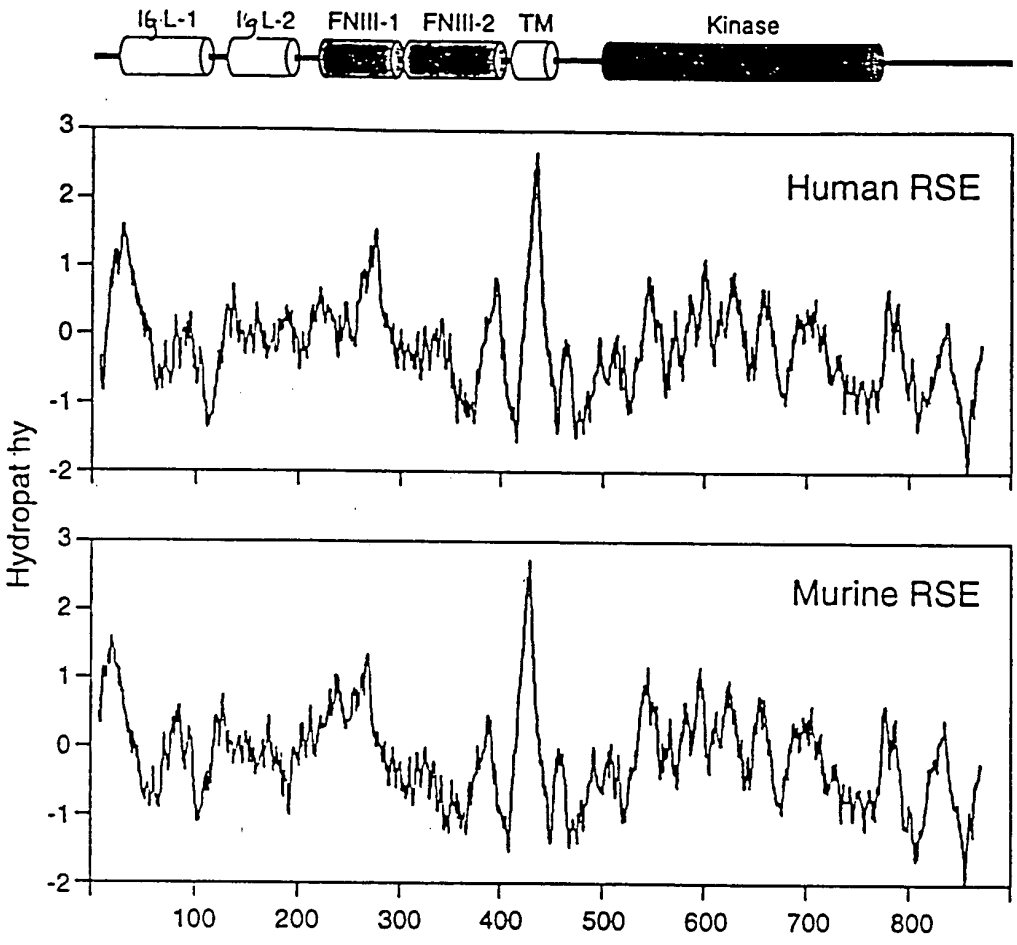
Ig L-1
Ig L-2
FNIII-1
FNIII-2
TM
Kinase
Human RSE
Murine RSE
Hydropat hy
3
2
1
0
-1
-2
100
200
300
400
500
600
700
800

FIGURE [4-1] 5A

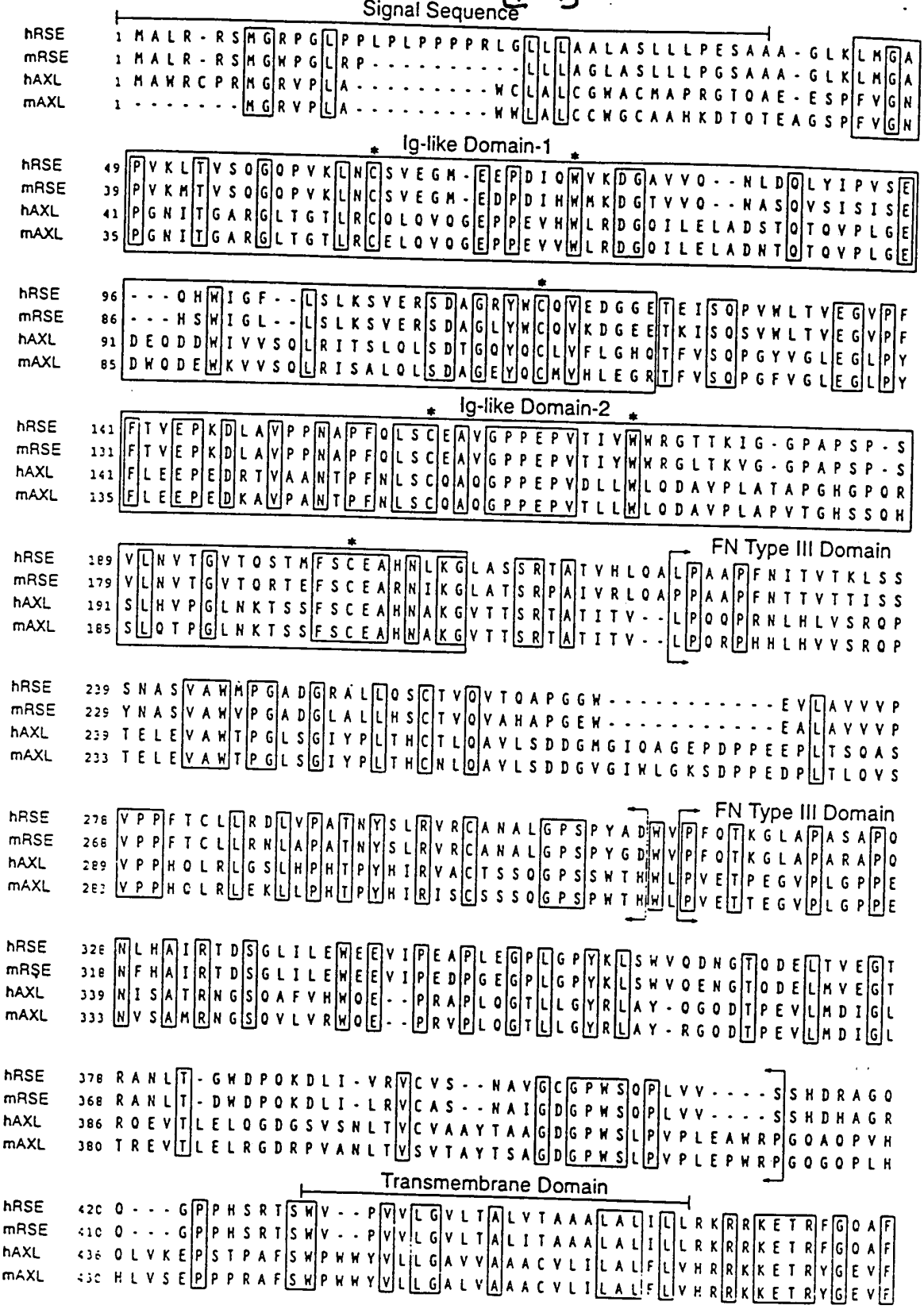
Signal Sequence
Ig-like Domain-1
Ig-like Domain-2
FN Type III Domain
FN Type III Domain
Transmembrane Domain
hRSE
mRSE
hAXL
mAXL

FIGURE [4-2] 5B

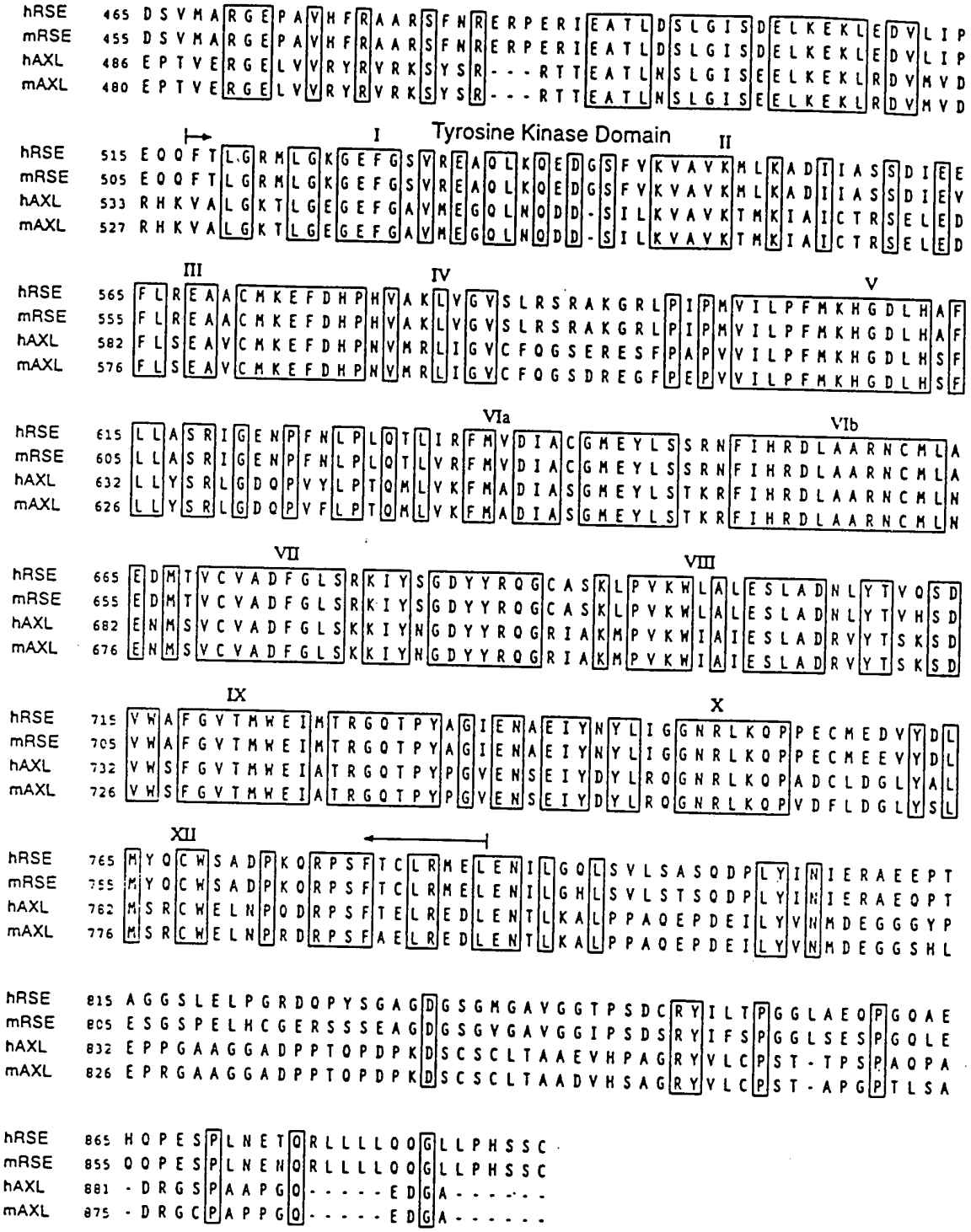
Tyrosine Kinase Domain
I
II
III
IV
V
VIa
VIb
VII
VIII
IX
X
XII
hRSE
mRSE
hAXL
mAXL

FIGURE [5] 6

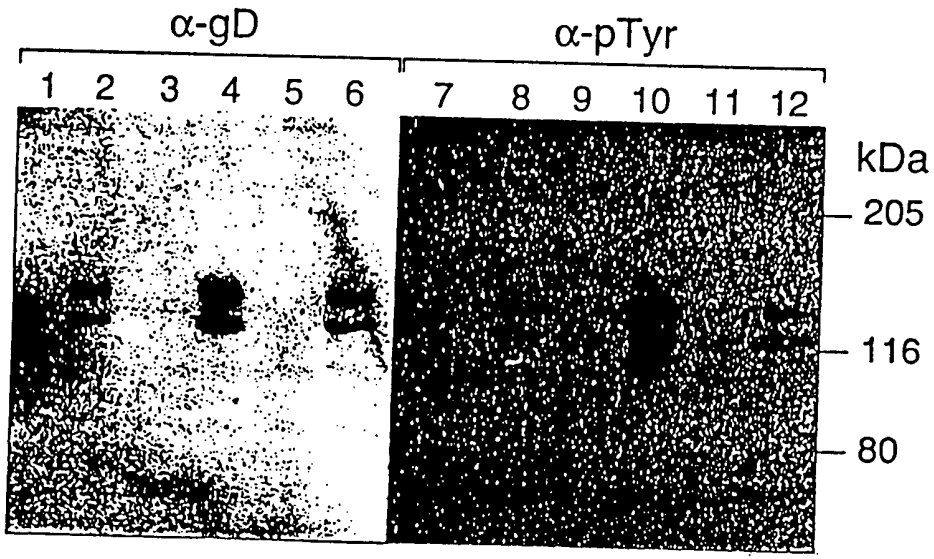

FIGURE [6] 7

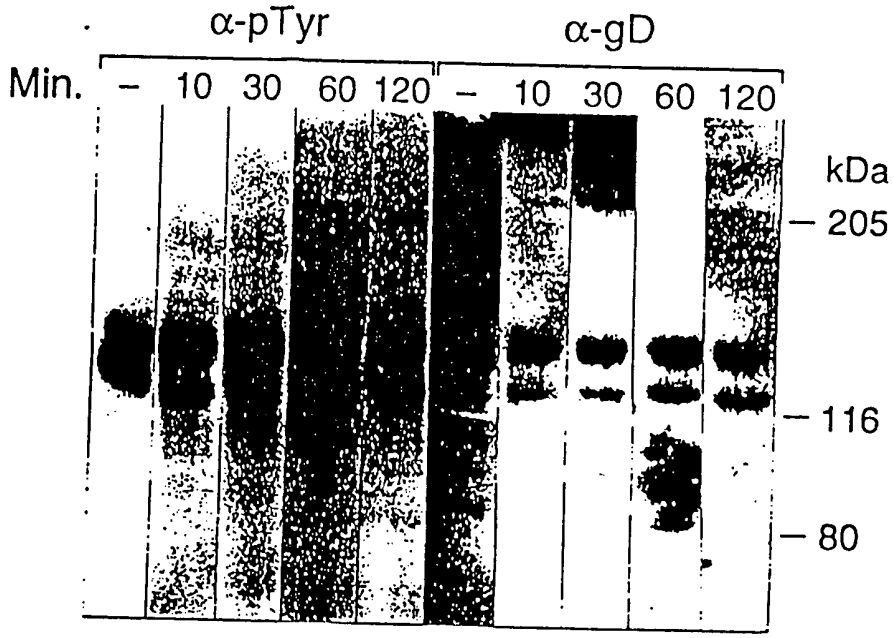

FIGURE [1A] 8A

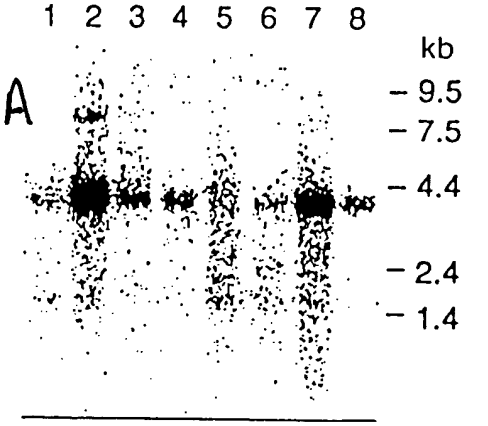

FIGURE [1B] 8B

FIGURE [A] 9A

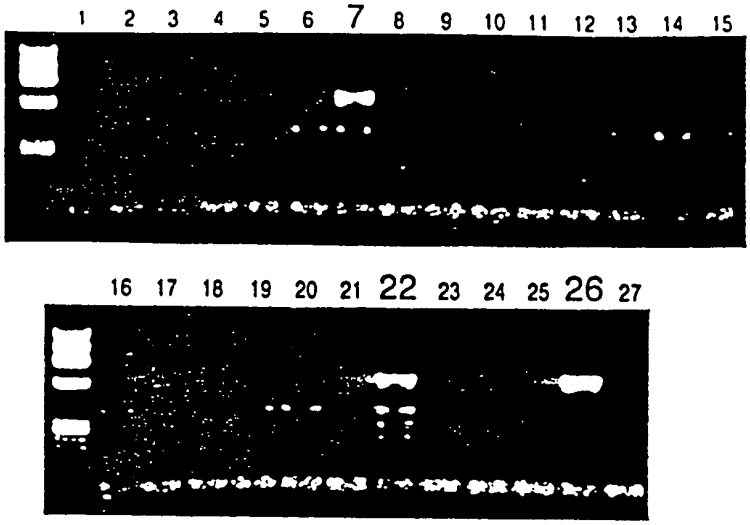

FIGURE [B] 9B

CHROMOSOME CONTENT OF SOMATIC CELL HYBRID PANEL

LANE #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
CELL LINE	312	334	423	507	683	734	750	756	803	811	852	860	862	867	904	909	931	940	967	968	983	1006	1049	1079	1099
Human Chromosome 1														•			•								•
2											•														
3			•	•								•												•	
4									•													•			
5	•			•	•	•	•	•	•			•	•	•	•	•	•	•	•	•	•	•	•	•	•
6								•				•			•	•									
7								•														•			
8									•	•						•			•			•			
9						•							•							•					
10												•									•				
11									•														•		
12				•	•			•							•										
13							•	•						•						•		•			•
14				•	•		•	•						•		•	•								
15							•															•			
16															•				•					•	
17										•							•								
18		•				•				•				•											
19					•		•	•				•		•								•			
20				•				•										•							
21					•			•				•			•		•								
22				•	•				•																•
X									•							•				•					
Y	•			•			•								•										

Human Chromosome

FIGURE [9.] 10

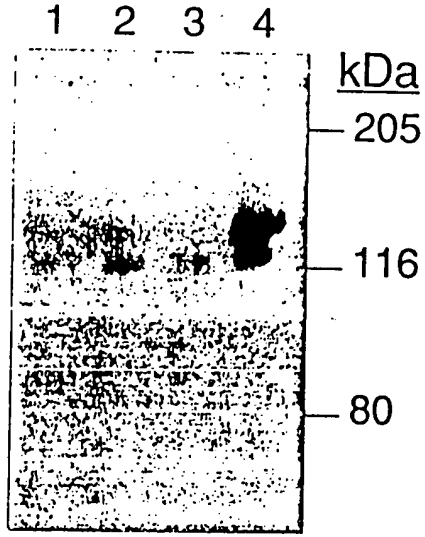

FIGURE [10A.] 11A

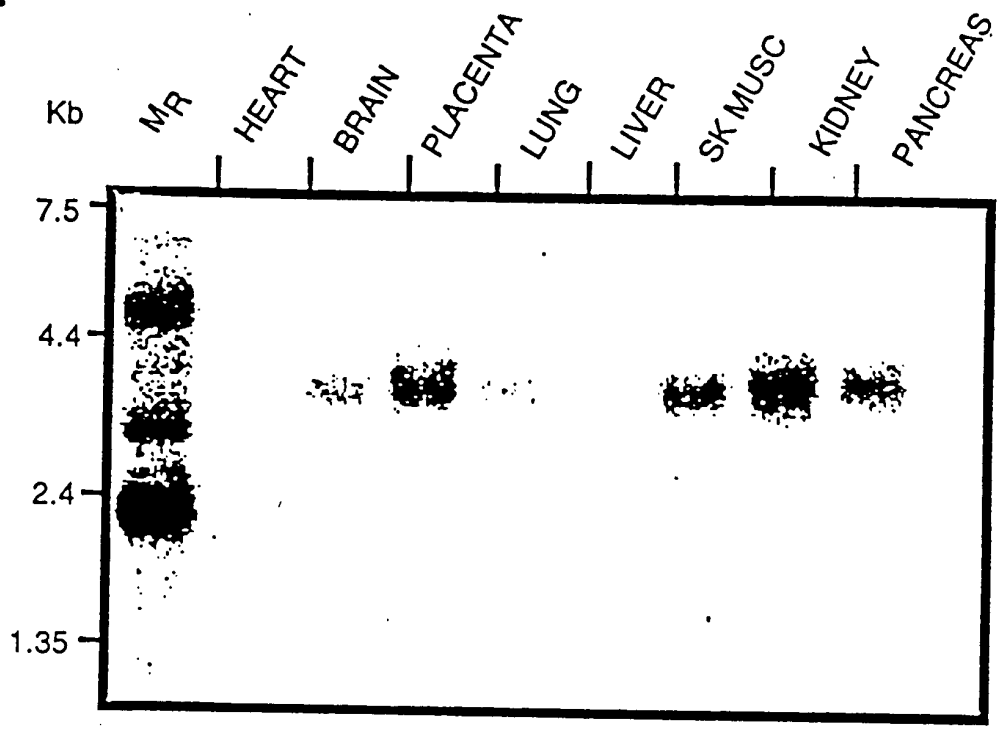

FIGURE [10 B.] 11B

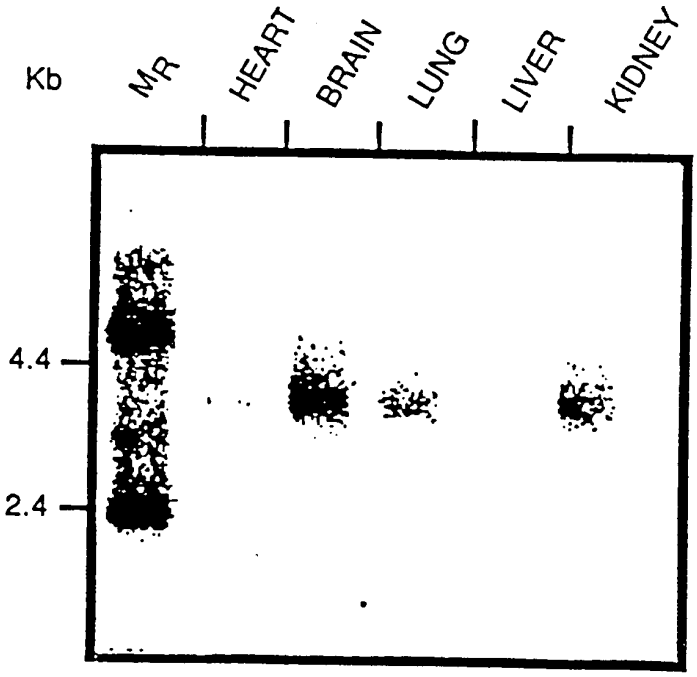

FIGURE [11A] 12A

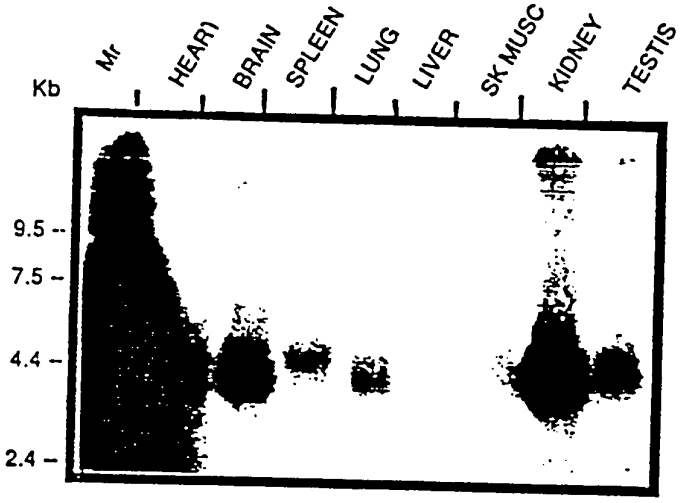

FIGURE [11B] 12B